PB85-211977

Exposure and Risk Assessment for Trihalomethanes (Chloroform, Bromoform, Bromodichloromethane, Dibromochloromethane)

Little (Arthur D.), Inc., Cambridge, MA

Prepared for

Environmental Protection Agency, Washington, DC

Nov 80

U.S. Department of Commerce
National Technical Information Service
NTIS

PB85-211977

United States
Environmental Protection
Agency

Office of Water
Regulations and Standards (WH-553)
Washington DC 20460

November 1980
EPA-440/4-81-018

Water

EPA

An Exposure and Risk Assessment for Trihalomethanes

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50272-101

REPORT DOCUMENTATION PAGE

1. REPORT NO. EPA-440/4-81-018

2.

3. Recipient's Accession No. PB85 211977/AS

4. Title and Subtitle

An Exposure and Risk Assessment for Trihalomethanes:
Chloroform, Bromoform, Bromodichloromethane, Dibromochloromethane

5. Report Date November 1980

6.

7. Author(s)

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8. Performing Organization Rept. No.

9. Performing Organization Name and Address

Arthur D. Little, Inc.
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Cambridge, MA 02140

10. Project/Task/Work Unit No.

11. Contract(C) or Grant(G) No.

(C) 68-01-3857
(G)

12. Sponsoring Organization Name and Address

Monitoring and Data Support Division
Office of Water Regulations and Standards
U.S. Environmental Protection Agency
Washington, D.C. 20460

13. Type of Report & Period Covered

Final

14.

15. Supplementary Notes

Extensive Bibliographies

16. Abstract (Limit: 200 words)

This report assesses the risk of exposure to chloroform, bromoform, bromodichloromethane, and dibromochloromethane. This study is part of a program to identify the sources of and evaluate exposure to 129 priority pollutants. The analysis is based on available information from government, industry, and technical publications assembled in November 1980.

The assessment includes an identification of releases to the environment during production, use, or disposal of the substance. In addition, the fate of trihalomethanes in the environment is considered; ambient levels to which various populations of humans and aquatic life are exposed are reported. Exposure levels are estimated and available data on toxicity are presented and interpreted. Information concerning all of these topics is combined in an assessment of the risks of exposure to trihalomethanes for various subpopulations.

17. Document Analysis a. Descriptors

Exposure
Risk
Water Pollution
Air Pollution
Effluents
Waste Disposal
Food Contamination
Toxic Diseases
Trihalomethanes
Chloroform
Bromoform
Dibromochloromethane
Bromodichloromethane

b. Identifiers/Open-Ended Terms

Pollutant Pathways
Risk Assessment

c. COSATI Field/Group 06F 06T

18. Availability Statement

Release to Public

19. Security Class (This Report) Unclassified

20. Security Class (This Page) Unclassified

21. No. of Pages 122

22. Price

(See ANSI-Z39.18)

See instructions on Reverse

OPTIONAL FORM 272 (4-77)
(Formerly NTIS-35)
Department of Commerce

EPA-440/4-81-018
November 1980

AN EXPOSURE AND RISK ASSESSMENT
FOR TRIHALOMETHANES:

Chloroform
Bromoform
Bromodichloromethane
Dibromochloromethane

by

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EPA Contract 68-01-3857

Monitoring and Data Support Division (WH-553)
Office of Water Regulations and Standards
Washington, D.C. 20460

OFFICE OF WATER REGULATIONS AND STANDARDS
OFFICE OF WATER AND WASTE MANAGEMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

FOREWORD

Effective regulatory action for toxic chemicals requires an understanding of the human and environmental risks associated with the manufacture, use, and disposal of the chemical. Assessment of risk requires a scientific judgment about the probability of harm to the environment resulting from known or potential environmental concentrations. The risk assessment process integrates health effects data (e.g., carcinogenicity, teratogenicity) with information on exposure. The components of exposure include an evaluation of the sources of the chemical, exposure pathways, ambient levels, and an identification of exposed populations including humans and aquatic life.

This assessment was performed as part of a program to determine the environmental risks associated with current use and disposal patterns for 65 chemicals and classes of chemicals (expanded to 129 "priority pollutants") named in the 1977 Clean Water Act. It includes an assessment of risk for humans and aquatic life and is intended to serve as a technical basis for developing the most appropriate and effective strategy for mitigating these risks.

This document is a contractors' final report. It has been extensively reviewed by the individual contractors and by the EPA at several stages of completion. Each chapter of the draft was reviewed by members of the authoring contractor's senior technical staff (e.g., toxicologists, environmental scientists) who had not previously been directly involved in the work. These individuals were selected by management to be the technical peers of the chapter authors. The chapters were comprehensively checked for uniformity in quality and content by the contractor's editorial team, which also was responsible for the production of the final report. The contractor's senior project management subsequently reviewed the final report in its entirety.

At EPA a senior staff member was responsible for guiding the contractors, reviewing the manuscripts, and soliciting comments, where appropriate, from related programs within EPA (e.g., Office of Toxic Substances, Research and Development, Air Programs, Solid and Hazardous Waste, etc.). A complete draft was summarized by the assigned EPA staff member and reviewed for technical and policy implications with the Office Director (formerly the Deputy Assistant Administrator) of Water Regulations and Standards. Subsequent revisions were included in the final report.

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ACKNOWLEDGMENTS

The Arthur D. Little, Inc. task manager for this study was Joanne Perwak. Other major contributors were Muriel Goyer (human effects), Judith Harris (Environmental Fate), Susan Coons (Environmental Fate), Douglas Wallace (biotic effects and exposure), Kate Scow (biological fate), Melba Wood (monitoring data), Joseph Fiksel (risk considerations), Jane Metzger (editor), and Alfred Wechsler (technical review). Irene Rickabaugh was responsible for typing and preparation of the final draft report.

CHAPTER I

EXECUTIVE SUMMARY

INTRODUCTION

The Monitoring and Data Support Division, Office of Water Regulations and Standards, U.S. Environmental Protection Agency is conducting an ongoing program to identify the sources of and evaluate the exposure to the 129 priority pollutants. This report assesses the exposure to and risk associated with trihalomethanes (chloroform, bromodichloromethane, dibromochloromethane, and bromoform). The summary is organized somewhat differently than the report, focusing on the risk considerations first since this section presents the major conclusions of the study.

HUMAN RISK CONSIDERATIONS

Chloroform has been shown to be carcinogenic in rats and mice; however, no evidence indicates mutagenicity in these species and evidence for teratogenicity is contradictory. Based on the multistage model for risk extrapolation, estimates of per capita lifetime risks of cancer ranged from 0.3×10^{-6} in a rural area with no water chlorination to 5.2×10^{-6} in an industrial area. An estimated lifetime risk of cancer for a child is 47×10^{-6} due to swimming in chlorinated pools, inhalation, and ingestion of chlorinated drinking water.

Risks due to other trihalomethanes cannot be quantitatively estimated. They have not been shown to be carcinogenic, although they are all considered potential mutagens. In addition, exposure levels due to dibromochloromethane, bromodichloromethane, and bromoform, are generally considerably lower than exposure levels for chloroform.

AQUATIC RISK CONSIDERATIONS

The information available regarding the effects and exposure of aquatic biota to trihalomethanes is insufficient to determine risk. However, it appears that levels observed in the environment are generally well below levels at which effects are observed.

HUMAN EFFECTS

Studies regarding trihalomethanes have concentrated on chloroform, since it is the most prevalent of the four chemicals being considered here.

Ingestion of 90-138 mg/kg of chloroform has been shown to induce both hepatic and renal tumors in experimental animals, although some experiments at lower dosages have yielded contradictory results. In addition, several epidemiological studies have suggested an association between ingestion of chlorinated drinking water and a higher incidence of cancer.

No indications of mutagenic activity of chloroform have been reported, and evidence of teratogenicity is conflicting. However, inhalation of chloroform by rats during days 6-15 of gestation resulted in a high incidence of fetal resorption and a few cases of acudate fetuses.

Species-, strain-, and sex-related differences exist with respect to the acute lethal effects of chloroform, although exposure to chloroform generally results in liver necrosis and kidney damage. In man, serious illness has been reported following ingestion of 5 ml, although ingestion of 120 ml of chloroform has been survived. Dermal contact produces burning pain within a few minutes of exposure and, depending upon dose, erythema, hyperamia, and vesication may also result.

Limited toxicologic information is available for bromoform, dibromochloromethane, and bromodichloromethane. However, because of structural similarities to chloroform, all three compounds are cause for concern with regard to carcinogenic effects. Preliminary results in lung adenoma bioassays with bromoform and dichlorobromomethane support this concern. In addition, all three trihalomethanes are mutagenic in the Ames test. To date, other adverse health effects have not been demonstrated and therefore, cannot be quantified.

HUMAN EXPOSURE

The chlorination of drinking water represents the largest source of exposure of chloroform to most humans in the United States, generally ranging from 0.02-0.2 mg/day. The maximum exposure due to food was estimated to be 0.04 mg/day. However, very scant data are available regarding levels of chloroform in food, and the 0.04 mg/day estimate is thought to be an upper range or maximum exposure. Inhalation exposure to chloroform is generally low; however in urban and highly industrialized areas exposures have been estimated to be 0.02 mg/day and 0.5 mg/day, respectively, and thus comparable with drinking water exposures in areas with chlorinated water supplies. Dermal exposure can also be comparable, primarily due to the rapid absorption of chloroform through the skin. Swimmers, especially children, may receive up to 1.1 mg/day via this route.

Exposure routes for the other trihalomethanes are believed to be limited to drinking water, though no data are available regarding levels in other media. Median exposures through drinking water are less than 0.01 mg/day for bromoform, dibromochloromethane, and bromodichloromethane. However, maximum exposures of up to 0.6 mg/day have been estimated.

BIOTIC EFFECTS

Acute lethality to aquatic organisms due to chloroform and bromoform generally occurs at concentrations greater than 10 mg/l, as measured by LC_{50} values. A chronic value and a 96-hr LC_{50} value for bromoform in the sheepshead minnow were reported to be 0.2 mg/l and 17.9 mg/l, respectively. No data are available regarding the toxicity of dibromochloromethane and bromodichloromethane to aquatic organisms.

BIOTIC EXPOSURE

Ambient concentrations of chloroform in surface water generally fall between 0.1 ug/l and 10 ug/l. Concentrations of 100 ug/l were exceeded only rarely, although monitoring data are limited. Concentrations of the other trihalomethanes were lower than chloroform, generally in the range of the detection limit.

MATERIALS BALANCE

Approximately 158,500 kkg of chloroform were commercially produced in the U.S. in 1978. The predominant use (about 90%) is as a feedstock for the manufacture of chlorodifluoromethane (Fluorocarbon-22). The pharmaceutical industry consumed about 3700 kkg (0.3%) and 42 kkg were used for pesticides (0.02%). Of the commercially produced chloroform, about 11,600 kkg (7.3%) are unaccounted for. A large part of this may be used in laboratories, and some represents chloroform in stockpiles. The remainder probably reflects uncertainties in estimates of the amounts produced and used for other purposes.

Chloroform is also inadvertently produced as a contaminant during commercial production of other products such as vinyl chloride monomer (VCM). About 2700 kkg were produced in this process in 1978. Small smounts of chloroform (54 kkg) are produced in the production of methyl chloride, methylene chloride, and carbon tetrachloride.

Chloroform is also produced inadvertently upon the reaction of chlorine with numerous organic precursors. It is produced in chlorinated drinking water, in the effluents of municipal and industrial wastewater; and in chlorinated industrial cooling water. The bleaching process in the pulp and paper industry accounts for the single largest source of this type, producing about 12,500 kkg of chloroform in 1978. The chlorination of drinking water, municipal wastewater, and industrial cooling water produced 912 kkg, 91 kkg, and 3460 kkg, respectively.

Chloroform may be produced as combustion product of leaded gasoline (970) kkg and as a decomposition product of trichloroethylene in the lower troposphere (430 kkg). In addition, it may be produced by marine algae, although such a production has not been quantified.

Of the identified environmental releases (20,600 kkg) of chloroform, 93% (or 19,200 kkg) were released to air. Of this, pulp and paper bleaching is the largest contributor, accounting for 63% of the air releases. About 17% was released as a result of chlorination of drinking water, municipal wastewaters and cooling tower waters. Losses from pharmaceutical uses accounted for about 8% of the releases to air. Releases from chloroform production and Fluorocarbon-22 production are relatively small, accounting for 2% and 1% of the total air releases, respectively. The remaining 9% is attributed to automobile exhaust, trichloroethylene manufacture, VCM production, pesticide use, and transportation and storage losses. It should be pointed out that there is a great deal of uncertainty in these estimates of releases due to lack of data.

Releases to water are relatively small (4% of the total). Again, pulp and paper bleaching appears to represent the major source to water (44%). The chlorination of water and the use of chloroform in the pharmaceutical industry represent 21% and 30% of the total, respectively. The remaining 5% is attributed to chloroform production and VCM production. No water discharges have been identified from Fluorocarbon-22 production.

The disposal of chloroform on land represents only 3% of the total known releases to the environment. About 59% of the amount placed in landfills is attributed to pharmaceutical operations, and 40% is attributed to disposal of solid waste from VCM manufacture. The remaining 1% is a result of solid waste from production of chloroform.

Information regarding the production and uses of bromoform, bromodichloromethane, and dibromochloromethane is very limited. The production of bromoform is thought to be less than 500 kkg, and its major use is as an intermediate in chemical synthesis. The other two trihalomethanes are thought to be produced only in laboratory quantities.

The major releases of these chemicals result from their production in water chlorination. Total releases of 17 kkg, 832 kkg, and 204 kkg, have been roughly estimated for bromoform, bromodichloromethane, and dibromochloromethane, respectively. It is expected that the greater portion of these amounts reach the atmosphere, as is the case for chloroform.

ENVIRONMENTAL FATE AND DISTRIBUTION

Trihalomethanes, especially chloroform, are commonly found in the natural waters of the United States. Levels in the open ocean appear to be in the range of 1-10 ug/1. The other trihalomethanes are not commonly detected, and when found are at lower concentrations than chloroform.

Chloroform is also found in ambient air, both indoors and outdoors. Continental background levels range from 0.04-0.13 ug/m^3, while marine background levels are somewhat higher. Levels in urban areas are highly variable, ranging from <0.05 ug/m^3 to 90 ug/m^3, with the maximum occurring in a highly industrialized area.

The fate of trihalomethanes is largely controlled by their volatility. While much of the chloroform is originally released to the air, that reaching water is rapidly volatilized. The half-life from a stirred aqueous solution is 20 minutes. The importance of hydrolysis, adsorption, bioaccumulation, and biodegradation appear low compared to volatilization.

Once reaching the atmosphere, chloroform, and other trihalomethanes probably travel considerable distances before degradation occurs. The lifetime in the troposphere has been estimated to be 2-3 months.

attributable primarily to reaction with hydroxyl radicals. Photochemical degradation of trihalomethane, as well as rainout are not expected to be important pathways.

Volatilization is also likely from soil surfaces. Biodegradation and adsorption are not likely to be important fate processes. Thus, trihalomethanes which are not volatilized are subject to rapid movement downward.

A partitioning model suggests that at equilibrium, the trihalomethanes would be primarily (>99%) in the air compartment. EXAMS (Exposure Analysis Modeling System, U.S. EPA, Athens, Ga.) also showed that volatilization was the dominant fate process in lakes and ponds. In rivers, physical transport dominated volatilization as a removal mechanism (over the short stretch of river modelled).

CHAPTER II

INTRODUCTION

The Office of Water Regulations and Standards, Monitoring and Data Support Division of the Environmental Protection Agency is conducting a program to evaluate the exposure to and risk of 129 priority pollutants in the nation's environment. The risks to be evaluated include potential harm to human beings and deleterious effects on fish and other biota. The goal of the task under which this report has been prepared is to integrate information on cultural and environmental flows of specific priority pollutants and estimate the risk based on receptor exposure to these substances. The results are intended to serve as a basis for developing suitable regulatory strategy for reducing the risk, if such action is indicated.

This document is an assessment of risks associated with exposure to trihalomethanes, including chloroform, bromodichloromethane, dibromochloromethane and bromoform. In an attempt to associate exposure to specific sources, the report also provides information on the production use, distribution, and fate of these chemicals. There are several difficulties in such an assessment which should be mentioned.

First, a significant route of human exposure is the inadvertent production of trihalomethanes that results during the chlorination of drinking water. This production is difficult to quantify from a materials balance point of view, however, the monitoring data for these chemicals is fairly extensive. Thus, while the exposure levels are fairly well documented, the total production of trihalomethanes in chlorination is not.

Secondly, at least some data on most aspects considered here can be found for chloroform. However, data on the other trihalomethanes is extremely sparse. The lack of toxicological data makes the consideration of risk of these chemicals inconclusive.

Finally, the carcinogenic risk of chloroform has been extensively considered by other authors. The ranges in the values of estimated risks give a good indication of the uncertainties involved in such estimations. We have included a discussion of the ranges involved and the various methods used in estimation of risk.

The following sections of the report are as follows:

- Chapter III contains information on the production (commercial and inadvertent), releases, and disposal of trihalomethanes.

- Chapter IV describes available monitoring data and considers the fate of trihalomethanes in various pathways.

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- Chapter V considers reported effect levels (for laboratory animals) and estimated exposure levels for humans.

- Chapter VI discusses reported effect levels and estimated exposure levels for biota.

- Chapter VII discusses risk to various subpopulations of humans and other biota.

CHAPTER III

MATERIALS BALANCE

A. INTRODUCTION

This chapter presents a materials balance for trihalomethanes, considering the processes by which these chemicals are produced, their various commercial uses, and the modes of disposition or disposal. At each stage in the life cycle of these chemicals, the amounts and forms of releases to the environment are characterized and the environmental compartments (air and water) initially receiving the pollutant release are identified.

A number of problems are encountered in attempting to develop a comprehensive materials balance for the trihalomethanes. Not all current production volumes, uses, and disposal practices are known with any degree of certainty, and in many cases only sparse information is available concerning environmental releases. Nevertheless sufficient information exists to characterize in general terms the environmental releases of these chemicals.

Of the trihalomethanes, chloroform is produced and consumed in a far greater volume than all of the other trihalomethanes combined. Consequently far more information is available concerning chloroform. A detailed analysis of chloroform production and use was recently published as a Level I Materials Balance by JRB Associates (1980) for the U.S. EPA Office of Toxic Substances. This report served as the major source document for the chloroform materials balance in this chapter and was supplemented by other literature and some new analysis in specific areas.

No comparable analysis has been done for bromoform, bromodichloromethane, or dibromochloromethane. Furthermore, the use of these chemicals is so limited that information concerning them is considered proprietary by the manufacturers and/or distributors. This situation severely limits the level of detail that could be achieved in the materials balance developed for these substances.

This chapter presents first a materials balance for chloroform by considering its commercial production and uses, its production as a contaminant, indirect production, and the environmental releases at various stages of its production and use. Then a materials balance is developed for the remaining trihalomethanes.

B. CHLOROFORM

1. Commercial Production and Use

a. Commercial Production

Chloroform is produced commercially by the successive chlorination of the methyl radical by one of two principal chlorination processes (using methane, or methanol as feedstocks), which can be controlled to produce methyl chloride, methylene chloride, and carbon tetrachloride, as well as chloroform. [Details of these processes are described by JRB Associates (1980).] In 1978 the methanol process accounted for 122,500 kkg (77%) of the chloroform produced, while the methane process accounted for 36,000 kkg (23%) (Table 1). Because of the flexibility of the production facilities to switch processes, there is an uncertainty of greater than ±10% (greater than ±15,850 kkg) associated with the total commercial production of 158,500 kkg of chloroform in 1978 (JRB Associates 1980).

Imports amounted to 7,670 kkg of chloroform in 1978 and 7,900 kkg were exported (JRB Associates 1980). The locations of chloroform production facilities and their capacities are shown in Figure 1.

b. Uses

The predominant consumptive use of chloroform is as feedstock for the manufacture of chlorodifluoromethane (Fluorocarbon-22 or F-22), though there is some uncertainty as to the exact amount of chloroform consumed in this manner. JRB Associates (1980) assumed that in 1978 90% of the chloroform produced was consumed as F-22 feedstock. Other estimates indicate that as much as 93% may have been consumed for this use in 1973 (NAS 1978).

The pharmaceutical industry is a consumer of approximately 3,700 kkg of chloroform for use as a solvent in extraction processes (JRB Associates 1980). An estimated 42 kkg of chloroform is used as pesticide. The use of chloroform as an industrial solvent, and in the textile and dye industries, was investigated by JRB Associates (1980) because of previous references to these categories of use (NAS 1978) and found to be insignificant and declining.

Of the commercially produced chloroform, about 11,600 kkg are unaccounted for. Some of this is used in laboratories and some represents chloroform in stock piles. The remainder may reflect uncertainty in the amounts used for other purposes.

c. Production as a Contaminant

Chloroform is produced as a contaminant during commercial production of other products. The same process that produces chloroform is used for the commercial production of methyl chloride, methylene chloride and carbon tetrachloride. The amount of chloroform included as impurities

TABLE 1. PRODUCTION AND USES/RELEASES OF CHLOROFORM, 1978

	Production (kkg)	
Commercial Production		159,000
Methyl Chloride Process	122,500	
Methane Process	36,000	
Loss during Production	500	
Imports		7,670
Production as Contaminant		2,733
Vinyl Chloride Monomer	2,679	
CH_3Cl, CH_2Cl_2, and CCl_4	54	
Chlorination of Water		3,466
Cooling Water	2,460	
Potable Water	912	
POTW[1]	91	
Swimming Pools	3[2]	
Bleaching of Paper Pulp		12,500[2]
Automobile Exhaust		965
Photodecomposition of Trichloroethylene		450
Marine Algae		(unknown)
TOTAL		186,784

TABLE 1. PRODUCTION AND USES/RELEASES OF CHLOROFORM, 1978 (Cont'd)

Uses/Releases (kkg)

	Air	Water	Land		
Feedstock for F-22 Production					142,700
Exports					7,900
Incinerated/Retained in Products/Storage					3,968
VCM Products				2,290	
Pharmaceutical Production				1,610	
F-11/F-12 Production (and others)				47	
$CHCl_3$ Production				17	
Pesticide Production				4	
Unaccounted for (including laboratory use and stockpiles)					11,600
Released to Environment	19,207	912	496		20,615
$CHCl_3$ Production	370[4]	14	6		
Pulp and Paper Bleaching	12,100[2]	400	---		
Chlorination of Water	3,245[3]	221	---		
Pharmaceutical Extractions	1,525	275	290		
Automobile Exhaust	965	---	---		
Trichloroethylene Decomposition	450	---	---		
VCM Production	187	2	200		
Transportation and Storage Loss	177	---	---		
F-22 Production	150	---	---		
Pesticides	38	---	---		
TOTAL					186,783

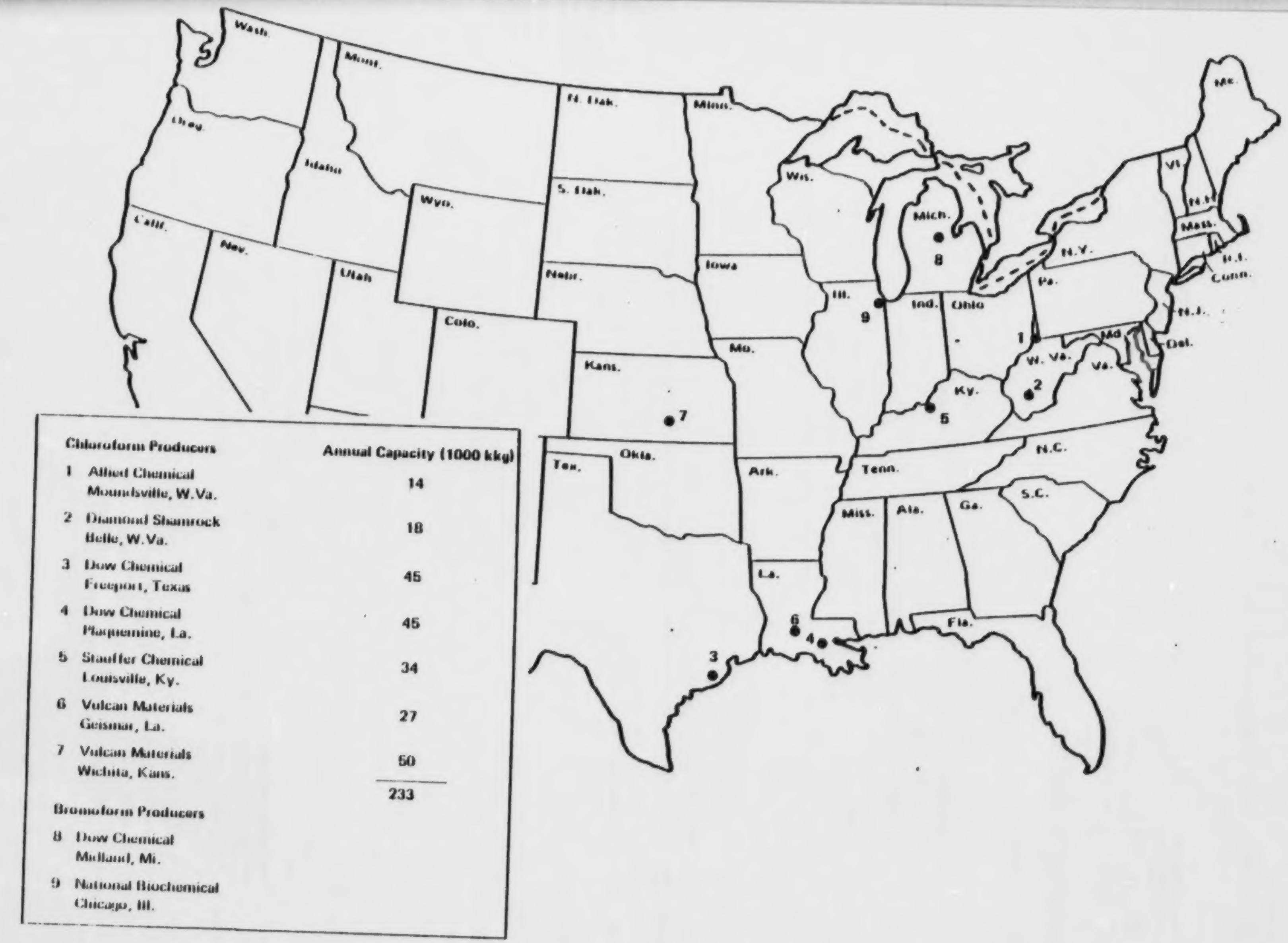
[1] Publicly Owned Treatment Works

[2] Arthur D. Little, Inc., estimate

[3] Arthur D. Little, Inc., after JRB Associates (1980)

[4] Average of JRB estimates of controlled (248 kkg) and uncontrolled (491 kkg) releases.

Source: JRB Associates (1980), except as otherwise noted


Wash.
Mont.
N. Dak.
Minn.
Me.
Oreg.
Idaho
S. Dak.
Wis.
Vt.
N.H.
Wyo.
Mich.
Mass.
Calif.
Nev.
Iowa
N.Y.
R.I.
Conn.
Utah
Nebr.
Ill.
Ind.
Ohio
Pa.
N.J.
Colo.
Mo.
Md.
Del.
Kans.
W. Va.
Va.
Ky.
Okla.
Tex.
Ark.
Tenn.
N.C.
Miss.
Ala.
Ga.
S.C.
La.
Fla.
1
2
3
4
5
6
7
8
9

Chloroform Producers	Annual Capacity (1000 kkg)
1 Allied Chemical Moundsville, W.Va.	14
2 Diamond Shamrock Belle, W.Va.	18
3 Dow Chemical Freeport, Texas	45
4 Dow Chemical Plaquemine, La.	45
5 Stauffer Chemical Louisville, Ky.	34
6 Vulcan Materials Geismar, La.	27
7 Vulcan Materials Wichita, Kans.	50
	233
Bromoform Producers	
8 Dow Chemical Midland, Mi.	
9 National Biochemical Chicago, Ill.	

Source: Arthur D. Little, Inc., based on JRB Associates (1980).

FIGURE 1 GEOGRAPHIC LOCATION OF TRIHALOMETHANE PRODUCERS IN THE U.S., 1978

in these products is estimated to be 54 kkg each year (JRB Associates 1980).

Chloroform is also produced during the manufacture of vinyl chloride monomer. JRB Associates (1980) estimated that this process contributed 2,679 kkg in 1978. Most of this is contained in the product, but some is lost during the process.

2. Indirect Production

a. Chlorination of Water

Chlorine reacts with organic precursors in water to form chloroform and other halomethanes (NAS 1978; Trussel and Umphres 1978; Norwood *et al*. 1980). The nature and amount of haloforms produced depends upon a number of factors, including water source (surface, groundwater), organic content, temperature, form and amount of chlorine added, etc. Annual chloroform production associated with municipal water supplies, municipal waste treatment facilities, and treatment of industrial cooling water has been estimated to be 912 kkg, 91 kkg, and 2,460 kkg, respectively (JRB Associates 1980).

b. Industrial Processes

Chloroform and associated halocarbons have been observed in the effluents of many industries. In some cases, the presence of these chemicals is believed to result from the direct use of the observed chemical in the industrial process (NAS 1978). However, in at least some cases, relatively large amounts of chloroform may be produced and released during the manufacture of another product.

The pulp and paper industry is recognized as a significant producer of chloroform released to the environment (NAS 1978). Estimates of the total annual release from this source have ranged from 1.4 kkg/year (based on concentrations in treated wastewater) to a global estimate of 300,000 kkg/year. If one assumes that about 50% of worldwide pulp and paper production occurs in the U.S. (Arthur D. Little, Inc., estimate), the chloroform releases in the U.S. amount to about 150,000 kkg each year.

The approach yielding the 1.4 kkg value is based on an assumed average chloroform concentration of 1,000 ug/l in finished effluent from the wastewater treatment plants (Lowenbach and Schlesinger Associates 1979). This approach does not account for the chloroform produced during the bleaching process and lost directly to the atmosphere during the rinsing stages, or the amount removed during treatment of the raw wastewater from the mill.

The global estimate is based upon an industry-wide average chlorine-to-chloroform conversion efficiency of 6% (Yung *et al*. 1975). JRB Associates Inc. (1980) report that 4.5% may be a more appropriate conversion efficiency, but also note that the validity of assuming a fixed chlorine-to-chloroform conversion rate is suspect. Unanalyzed factors that contribute to uncertainty in this regard include process and equipment variations from one mill to another, differences in processing related to types of wood chips used, and lack of detailed knowledge of the functional groups within the lignins that contribute to formation of chloroform.

Though no comprehensive study of chloroform formation by the pulp and paper industry has been conducted to date, some portions of the problem have been investigated. In 1977, the National Council of the Paper Industry for Air and Stream Improvement (NCASI) monitored effluents at 11 pulp mills with bleach plants (NCASI 1977). The plants were selected with a view toward picking bleaching sequences representative of the industry as a whole (Andre Caron, NCASI, personal communication, May 1980). An average of 0.37 kg of chloroform (per kkg of pulp bleached) was found in the untreated mill effluent. Ninety-five percent of the chloroform was removed during treatment (aerated lagoons) of the mill wastes prior to discharge to natural waterways. Most of the reduction was due to vaporization of chloroform to the atmosphere during treatment. On the basis of NCASI (1977), JRB Associates (1980) calculated that 6,700 kkg of chloroform are produced in the untreated mill effluent.

The NCASI (1977) study did not directly address the question of overall conversion efficiency of Cl_2 to chloroform within the mill. However, preliminary laboratory experiments conducted in conjunction with the study indicated that bleaching with hypochlorite would result in a 1.0% conversion of chlorine to chloroform while bleaching with chlorine water resulted in a 0.17% conversion factor. These experiments were reportedly set up to simulate the bleaching process within various pulp mills (Robert Claeys, NCASI, personal communication, May 1980).

Thus, the above information suggests that previous estimates of conversion rates have erred on the high side. JRB Associates (1980) reported the total amount of chlorine (both Cl_2 and hypochlorite, NaOCl) used in the paper products industry in 1977 as 1.25 million kkg, but gave no estimate of the quantity used for purposes other than bleaching of pulpwood. Because of the uncertainties regarding the rate of chlorine conversion to chloroform in cooling water applications, as well as in the bleaching process, and uncertainties regarding the chemical form of the chlorine consumed, it is assumed for this materials balance that 1% of the chlorine consumed annually is converted in pulp mills to yield 12,500 kkg of chloroform. However, it must be noted that these estimates are based upon limited laboratory testing. When this is compared with the 6,700 kkg of chloroform production accounted for by JRB Associates in the raw wastewater from the mills, the 5,800 kkg difference is believed to represent an estimate of the amount of chloroform produced within the mills that escapes to the atmosphere during pulp rinsing and processing stages, but prior to the discharge of the mill effluents to the waste treatment plant. For purposes of the materials balance, 12,500 kkg is estimated to be the total amount of chloroform produced by pulp mills.

c. Automobile Exhaust

The combustion of leaded gasoline produces small quantities of chloroform. The details of the formation process are not known, but JRB Associates (1980) calculated an assumed upper limit on this production of 965 kkg per year, assuming that ethylene dichloride is the sole source of chloroform in automobile gas, and that yields from this source are as much as 1% of the ethylene dichloride combusted.

d. Atmospheric Formation

Laboratory experiments have shown that chloroform can be formed from the degradation of trichloroethylene under conditions simulating those found in the lower troposphere (Lowenbach and Schlesinger Associates 1979). Based on laboratory work and their own estimates of trichloroethylene released to the atmosphere, JRB Associates (1980) calculated that 450 kkg of chloroform are produced annually by this mechanism, although a high degree of uncertainty is associated with this number.

e. Marine Sources

Chloroform has been observed in marine waters and in marine algae (NAS 1978). However, the mechanisms for its production in marine algae are not thoroughly understood, and the distribution of chloroform in marine waters suggests possible anthropogenic rather than natural sources. Though the National Academy of Sciences (NAS 1978) concluded that marine sources are negligible, the issue remains unresolved. No estimate of marine production can be made at present.

3. Environmental Releases of Chloroform

a. Releases During Commercial Production and Use

Environmental releases of chloroform occur during its commercial production and use and during transportation and storage. Between 248 kkg (controlled) and 492 kkg (uncontrolled) of chloroform are believed to be emitted to the atmosphere during the commercial production of chloroform. Some 17 kkg of chloroform are incinerated in sludge, 14 kkg are discharged to water, and 6 kkg are deposited on land during commercial production (JRB Associates 1980).

Only 150 kkg of chloroform are emitted into the atmosphere by the process that accounts for the largest consumptive use of chloroform, 142,700 kkg consumed as a feedstock for F-22. No releases to land or water from this process have been identified (JRB Associates 1980).

The pharmaceutical industry accounts for the largest release of commercially produced chloroform. Some 1,525 kkg are estimated to be released to air, 275 kkg to water, 290 kkg to land, and some 1,610 kkg are incinerated with waste products. The uncertainties associated with all of these estimates are high (JRB Associates 1980).

The use of chloroform as a pesticide (fumigant) results in release of 38 kkg (±11%) to the atmosphere and the incineration of 4 kkg (JRB Associates 1980).

A detailed description of the release of chloroform present as a contaminant in methyl chloride, methylene chloride, and carbon tetrachloride, and their endproducts is given by JRB Associates (1980). These releases are dispersed and account for only 10 kkg of chloroform annually.

The chloroform produced as a byproduct of vinyl chloride monomer (VCM) manufacture is also described by JRB Associates (1980). Their calculations indicate that about 190 kkg (± more than 100%) are emitted to air, and 200 kkg (+130%, -71%) are deposited in landfill. Water discharges were not calculated, and 2,290 kkg (±5%) were assumed to be incinerated.

b. Releases from Indirect Production

The largest environmental release of chloroform from a single category arises from the pulp and paper bleaching industry (see Table 1). Some 72% (12,500 kkg,) of the total estimated environmental loading from indirect production (17,381 kkg) is attributed to this source. Approximately 400 kkg (5% of the 6,700 estimated in untreated effluent) are estimated to be discharged to surface waters and the remainder (12,100 kkg) are estimated to be released to the atmosphere.

The next largest release is from chlorination of water, which includes cooling water, municipal water supply, and municipal wastewater, each of which are discussed by JRB Associates (1980) and shown in Table 1. The amounts produced in these processes in 1978 are estimated to be 2460 kkg, 912 kkg, and 91 kkg, respectively, most of which is released to the atmosphere.

Swimming pools have been found to contain high concentrations of trihalomethanes. Freshwater pools tend to have higher concentrations of chloroform, while saltwater pools have higher levels of bromoform (Beech et al. 1980). If the total volume of water in U.S. swimming pools is assumed to be 2.6 x 10^{11} liters, about equally distributed between the North and the South (3-month and 5-month season, respectively), a release rate to the atmosphere of 3.3 kkg/year can be calculated for chloroform (Arthur D. Little, Inc., estimate). Although this constitutes a relatively small contribution to the materials balance, it may present a significant exposure to humans because of the direct full-body contact of those who swim. The total environmental release of chloroform from the chlorination of water is estimated to be 3,466 kkg, of which 3,245 kkg are emitted to the atmosphere and 221 kkg are discharged to water (JRB Associates 1980; Arthur D. Little, Inc., estimates).

All of the estimated chloroform production from automobile exhausts (965 kkg) and atmospheric photodecomposition of trichloroethylene (450 kkg) is released to the atmosphere.

c. Releases of Chloroform That are Unaccounted For

Some 11,600 kkg of commercially produced chloroform are unaccounted for in the materials balance. Although there is considerable uncertainty regarding this number, a large portion is probably used in laboratories and the rest is in stock piles. It is quite likely that the predominant release will be to the atmosphere, although it is unquantified. A major deviation from the conclusions of this section would occur if an undetected, significant use resulted in significant releases to other compartments.

C. BROMOFORM, BROMODICHLOROMETHANE, AND DIBROMOCHLOROMETHANE

1. Commercial Production and Use of Bromoform

In contrast to chloroform, which is commercially produced in large quantities and has been the subject of considerable study, bromoform, bromodichloromethane, and dibromochloromethane are neither produced nor used in large quantities, and have not been extensively studied. Bromoform is commercially produced by the Dow Chemical Company and by National Biochemical Corporation in plants located in Midland, Michigan, and Chicago, Illinois (see Figure 1). It is only one of many chemicals known to be produced at these plants, and information is not available on either the capacity or the actual volume of bromoform production at these plants. The total production of bromoform in 1975 was estimated to be less than 500 kkg (NAS 1978).

Information on bromoform use is also sparse. The major use of the chemical is as an intermediate in the synthesis of other chemicals, for example, as a chain transfer agent in the preparation of certain polymers (NAS 1978). Other uses cited by Standen (1963) include use as a heavy fluid in solids separation, and as a gage fluid.

Bromoform has pharmacologic action as a sedative and antitussive agent, but the extent of its use in these applications is undetermined. There are indications that bromoform was formerly used as a sedative (Strecher et al. 1968). Bromoform was not cited in U.S. Pharmacopeia (1978), a compendium of pharmacological agents. A fraction of the bromoform produced by the Dow Chemical Company may be used in pharmaceutical applications (SRI 1979).

Bromoform has also been formulated into flame-retardant compositions for cellulosic textile fabrics. Use of bromoform is believed to be limited in this application because after bromoform-based flame-retardant fabric finishes have been applied, the fiber may become stiff or discolored (Standen 1964). As a result, other formulations that are flame retardant and retain fiber character are considered preferable.

2. Commercial Production and Use of Bromodichloromethane and Dibromochloromethane

Bromodichloromethane and dibromochloromethane are synthesized by the treatment of chloroform with a more than stoichiometric quantity of anhydrous aluminum bromide or hydrogen bromide in the presence of a catalyst. The final steps in the process include a cool water wash to remove inorganic material and distillation of the final product (Standen 1978).

Data on the amounts of dibromochloromethane and bromodichloromethane produced are unavailable, but it has been estimated that these chemicals are commercially produced in laboratory quantities only (NAS 1978). They are distributed by Freeman Industries, Inc.; PRC, Inc.; and Aldrich Chemical Company. A major fraction of the Freeman Industries supply is imported (Sales representative, Freeman Industries, personal communication, 1980). Some portion may also be obtained domestically. These chemicals are sold for laboratory use, and no commercial use has been identified (NAS 1978).

3. Indirect Production

Bromoform, dibromochloromethane, and bromodichloromethane are all found in chlorinated waters in association with chloroform, and are believed to be produced as a result of the chlorination process (Rook 1976; Bellar et al. 1974). In order to estimate the quantity of these lesser trihalomethanes that is produced in association with the chlorination process, the generating mechanism is assumed to be similar to the one that produces chloroform. The generation rates are also assumed to be proportional to the relative concentrations of these chemicals found in the water supply as reported by U.S. EPA (1978): bromoform concentration is equal to 0.005 of the chloroform concentration; bromodichloromethane equals 0.24 times chloroform concentration; and dibromochloromethane equals 0.059 times chloroform concentration. When these ratios are applied to the 3,466 kkg of chloroform generated by water chlorination (see Table 1), the following estimates for 1978 have been calculated:

Bromoform	17 kkg
Bromodichloromethane	832 kkg
Dibromochloromethane	204 kkg

4. Environmental Releases

The environmental releases of bromoform, bromodichloromethane and dibromochloromethane are not defined any better than are their production and uses. Most commercially produced bromoform is used as a chemical intermediate and either decomposed or recycled. The 17 kkg of bromoform produced in association with chlorination of water could constitute the major environmental release. The commercially produced "laboratory quantities" of bromodichloromethane and dibromochloromethane are small in comparison with the amounts of these compounds that are believed to be generated as a result of chlorination of water and released directly into the environment (832 kkg and 204 kkg, respectively). Table 2 summarizes the available information concerning the production and uses/releases of these chemicals.

D. SUMMARY

Trihalomethanes are released into the environment during commercial production and use, their production as contaminants in other commercially produced products, and their indirect production as a result of chlorination, and other processes, and possibly through natural production by marine algae. The chloroform budget is more than 100 times larger than the budget of the next most abundant trihalomethane, and has, therefore, received much more attention in the literature than the others. There are still major areas of uncertainty concerning the magnitude of production, use, and release rates so that it is necessary to estimate many values for use in a materials balance for chloroform. In recent work on chloroform, JRB Associates (1980) have summarized the existing knowledge and reduced the uncertainty associated with many of these estimates. No comparable work exists for bromoform, bromodichloromethane, and dibromochloromethane. These substances are produced in relatively small quantities, which are not important commercially so that routine statistics on production and use are unavailable. The information that does exist is scanty and yields only the most rudimentary materials balance.

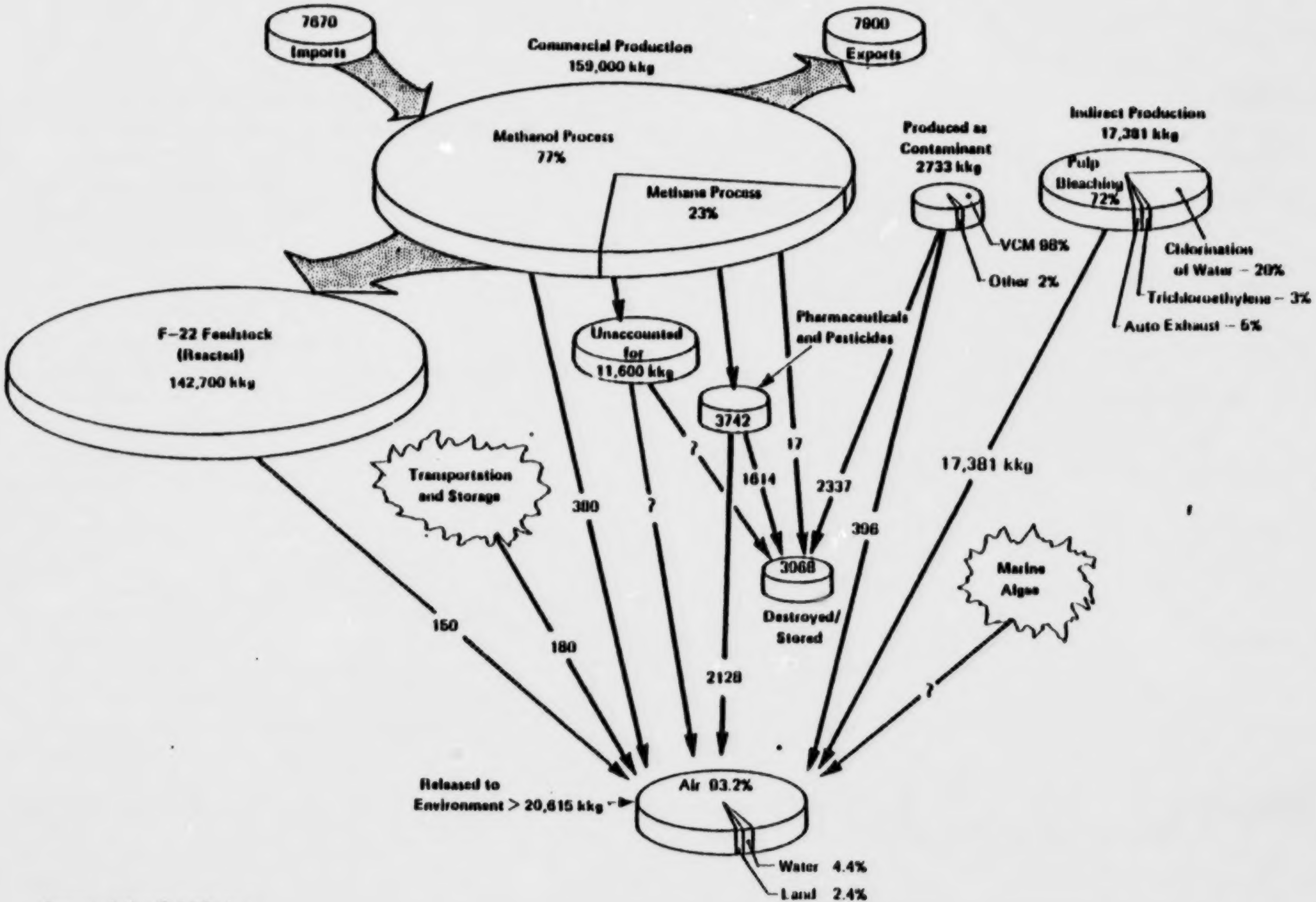
Figure 2 summarizes the materials balance for chloroform. The total chloroform budget is estimated to be on the order of 187,000 kkg/year. Imports and exports nearly balance each other at 4% of the total chloroform budget. Commercial production accounts for 85% of production, and 1.5% of production occurs as a contaminant in other products. Indirect sources account for 9.3% of total production. The largest uncertainty with apparent environmental significance on the production side of the budget is associated with the indirect sources (chlorination of water, bleaching of paper pulp, automobile exhaust, photodecomposition of trichloroethylene in the atmosphere, and marine algae). No estimate is available for the contribution of marine algae.

The major use of commercially produced chloroform is the production of chlorodifluoromethane (F-22), accounting for 76% of the total budget (90% of commercial production). Some 2% of the total budget is destroyed (by incineration) or retained in storage, and 11% of the total budget is released to the environment. JRB Associates (1980) estimated that 11,600 kkg chloroform (more than 6% of the total budget) was channeled to "laboratory use and stockpiles," and no information is available regarding the amount released or destroyed from this use.

TABLE 2. PRODUCTION AND USES/RELEASES OF THE LESSER TRIHALOMETHANES BROMOFORM, BROMODICHLOROMETHANE, AND DIBROMOCHLOROMETHANE, 1978

Category/Source	Annual Budget (kkg) Production	Annual Budget (kkg) Uses/Releases
Bromoform		
Commercial Production of $ChBr_3$	<500	--
Aqueous Production	17	--
Marine Algae Production	unknown	--
Chemical Intermediates	--	<500
Released Directly to Water and Air from Aqueous Production	--	17
	517	517
Bromodichloromethane		
Commercial Production	Laboratory Quantities	--
Aqueous Production	832	--
Research	--	Laboratory Quantities
Released Directly to Water and Air from Aqueous Production	--	832
	>832	>832
Dibromochloromethane		
Commercial Production	Laboratory Quantities	--
Aqueous Production	204	--
Research	--	Laboratory Quantities
Released Directly to Water and Air from Aqueous Production	--	204
	>204	>204

Source: NAS, 1978, Arthur D. Little, Inc., estimate, 1980.


7670
Imports
Commercial Production
159,000 kkg
7800
Exports
Methanol Process
77%
Methane Process
23%
F-22 Feedstock
(Reacted)
142,700 kkg
Unaccounted
for
11,600 kkg
3742
Pharmaceuticals
and Pesticides
Produced as
Contaminant
2733 kkg
VCM 98%
Other 2%
Indirect Production
17,381 kkg
Pulp
Bleaching
72%
Chlorination
of Water – 20%
Trichloroethylene – 3%
Auto Exhaust – 5%
Transportation
and Storage
300
?
?
1614
17
2337
396
17,381 kkg
3068
Destroyed/
Stored
Marine
Algae
150
180
2128
?
Released to
Environment > 20,615 kkg
Air 93.2%
Water 4.4%
Land 2.4%

Source: Arthur D. Little, Inc.

FIGURE 2 MATERIALS BALANCE FOR CHLOROFORM

Of the 20,600 kkg of chloroform identified as being released to the environment each year, 93% (or 19,200 kkg) is released to the air, 5% to the water, and 2% to the land. The single largest contribution to known environmental releases is 12,500 kkg from pulp and paper bleaching, accounting for 60% of the environmental releases tabulated. The largest unquantified source to the environment is the contribution from the unaccounted for "laboratory use and stockpile" category.

The largest source of atmospheric and aquatic releases of chloroform is pulp and paper bleaching, accounting for approximately 12,000 kkg chloroform in air emissions each year or nearly two-thirds of known atmospheric releases and 400 kkg in aquatic discharges or 44% of known releases to water. Chlorination of water is believed to contribute 17% (about 3200 kkg) of atmospheric emissions of chloroform, and 24% (about 220 kkg) of total known aqueous discharges. Major sources to land include the pharmaceutical industry (about 290 kkg) and production of vinyl chloride monomer (200 kkg).

Such analyses contain considerable uncertainties and these releases have been estimated as carefully as possible, often on the basis of very limited data. Therefore, the estimated releases should be considered in that light.

The limited information available concerning the other three trihalomethanes indicates that the predominant environmental release results from their production in association with water chlorination. No environmental releases due to their commercial production and use have been identified.

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CHAPTER IV

DISTRIBUTION IN THE ENVIRONMENT

A. INTRODUCTION

This chapter describes the important physicochemical properties of the trihalomethanes (Section B), provides detailed information on observed ambient levels of the chemicals (Section C), describes the important pathways and degradation routes in the environment (Section D), and gives the results of two different modeling efforts that were designed to assist in the assessment of the major transport pathways (Section E). A summary statement covering all aspects is provided in Section F.

Modeling of the fate of trihalomethanes, specifically chloroform, in environmental media was undertaken in order to illustrate important aspects of the chemical's fate and transport in selected environmental scenarios. One model predicts the expected distribution of chloroform in each environmental compartment (air, water, soil, sediment, biota) under the assumption that all phases are in equilibrium. This was done in order to determine the tendencies of this chemical to be transported in the environment. The second model used is EPA's EXAMS (Exposure Analysis Modeling System; U.S. EPA SERL, Athens, Ga.), which analyzes aquatic fate for various environmental scenarios.

B. PHYSICAL AND CHEMICAL PROPERTIES

Table 3 summarizes the available basic chemical and physical property data that are directly relevant to the environmental fate of the trihalomethanes. Of particular significance in terms of partitioning within the environment are the vapor pressure, the water solubility, and the octanol-water partition coefficient. Complete or nearly complete data were found for only chloroform and bromoform. For the other two trihalomethanes, the actual available data were minimal.

However, for the environmentally important properties, the difference between the values for chloroform and those for bromoform large, and it is reasonable to expect that values for bromodichloromethane and dibromochloromethane will fall in the range defined by those for $CHCl_3$ and $CHBr_3$. Thus, the important properties of the mixed trihalomethanes can be estimated with a considerable degree of confidence.

Because of the importance of volatility in determining environmental fate, the vapor pressure data were reviewed for bromoform and chloroform. Figure 3 shows the temperature dependence of the vapor pressure for these two species. The corresponding regression equations are:

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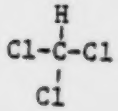
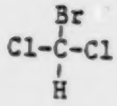
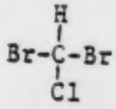
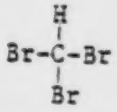
TABLE 3. BASIC PHYSICAL AND CHEMICAL PROPERTIES OF TRIHALOMETHANES

Property	Trihalomethanes			
	Chloroform	Bromodichloromethane	Dibromochloromethane	Bromoform
Formula	$CHCl_3$	$CHBrCl_2$	$CHBr_2Cl$	$CHBr_3$
	 $\mathrm{Cl}-\overset{\mathrm{H}}{\underset{\mathrm{Cl}}{\mathrm{C}}}-\mathrm{Cl}$	 $\mathrm{Cl}-\overset{\mathrm{Br}}{\underset{\mathrm{H}}{\mathrm{C}}}-\mathrm{Cl}$	 $\mathrm{Br}-\overset{\mathrm{H}}{\underset{\mathrm{Cl}}{\mathrm{C}}}-\mathrm{Br}$	 $\mathrm{Br}-\overset{\mathrm{H}}{\underset{\mathrm{Br}}{\mathrm{C}}}-\mathrm{Br}$
Molecular Weight	119.4	163.8	208.3	252.8
Melting Point (°C)	-63.5 [1]	---	---	8.3 [1]
Boiling Point (°C)	61.2 [1]	89-90 @ 742 mm Hg [1]	118-120 @ 742 mm Hg [1]	147.5 [1]
Vapor Pressure at 25°C	190 mm Hg [2] 25% (v/v)	ca 50 mm Hg [3] 7% (v/v)	ca 20 mm Hg [3] 3% (v/v)	6.3 mm Hg [2] 0.8% (v/v)
Water Solubility at 25°C	7800 mg/l [4] 65×10^{-3} M	5000 [5]	6000 [5]	1250 mg/l [6] 4.9×10^{-3} M
Octanol-Water Partition Coefficient	90 [7]	250 [8]	250 [8]	ca 370 [9]
Henry's Law Constant	2900 [10]	2000 [8]	2000 [8]	1300 [10]

[1] Hodgman (1962).

[2] Interpolated from Figure 3, by use of the data of Hodgman (1962).

[3] Arthur D. Little, Inc. estimate from b.p. data, assuming a H Δ of 8.7 kcal/mole, which is average of ΔH_{vap} for $CHCl_3$ (7.9 kcal/mole) and $CHBr_3$ (9.6 kcal/mole).

[4] Lyman (1978).

[5] Assumed solubility of 30×10^{-3} M, average of value for $CHCl_3$ and $CHBr_3$.

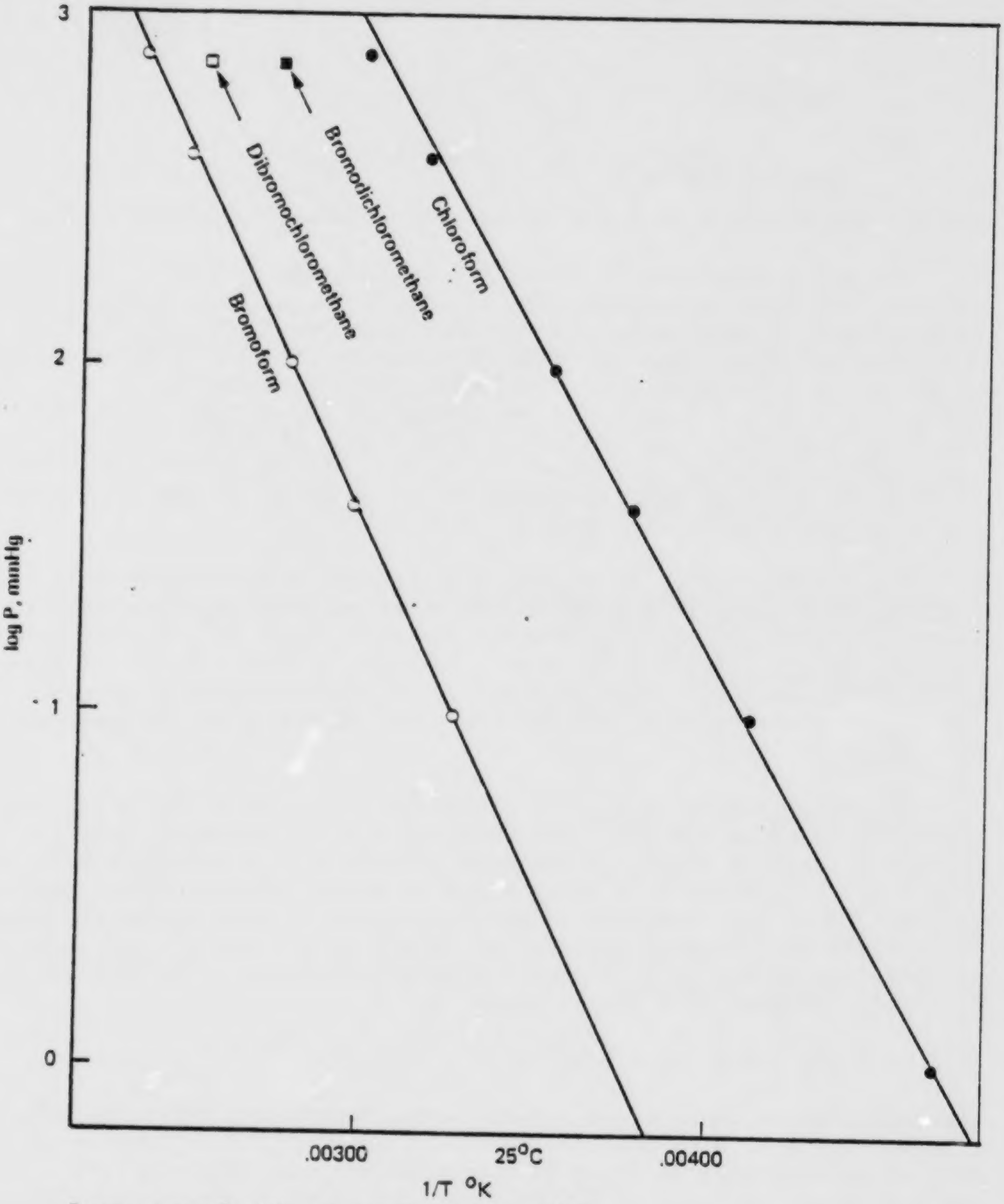
[6] Stacher *et al*. (1968).

[7] Hansch and Leo (1979).

[8] Estimated as intermediate value for $CHCl_3$ and $CHBr_3$.

[9] Estimated from water solubility by method of Hansch *et al*. (1968).

[10] Ratio of vapor pressure in (mm Hg) to water solubility (mM) at 25°C.



Source: Arthur D. Little, Inc., based on Hodgman (1962).

FIGURE 3 VAPOR PRESSURES OF TRIHALOMETHANES AS A FUNCTION OF TEMPERATURE

Chloroform:

$$\log P = \frac{-1738}{T} + 8.11, \ r = 0.9997$$

Bromoform:

$$\log P = \frac{-2090}{T} + 7.83, \ r = 0.9999$$

where P equals vapor pressure (mm Hg) and T equals temperature (°K).

The vapor pressures of chloroform and bromoform at 25°C were calculated from these equations. The slopes of these lines correspond to latent heats of vaporization of 7.9 kcal/mole for chloroform and 9.6 kcal/mole for bromoform. In order to estimate the 25°C vapor pressures of the mixed trihalomethanes, the latent heat of vaporization was estimated to be 8.7 kcal/mole, the average of the corresponding values for $CHCl_3$ and $CHBr_3$. The estimated latent heat of vaporization (ΔH_{vap}) was then combined with the reported boiling point data (Hodgman 1962) in order to estimate vapor pressures of 50 mm Hg for bromodichloromethane and 20 mm Hg for dibromochloromethane at 25°C.

The probable range of solubilities for the mixed bromo/chloro trihalomethanes may be defined by the 65 mM saturation concentration for chloroform in water (Lyman 1978) and the 4.9 mM value for bromoform (Stecher _et al_. 1968). An average solubility of about 30 mM was estimated for the mixed trihalomethanes. This would correspond to about 5000 mg/l of bromodichloromethane and about 6000 mg/l of dibromochloromethane at saturation.

The octanol-water partition coefficient provides a useful indication of tendencies for water-sediment and water-lipid partitioning. Literature data on this property were available only for chloroform (90, Hansch and Leo 1979). The value shown in Table 3 for bromoform was estimated from that compound's water solubility, according to the linear free-energy relationship approach of Hansch _et al_. (1968). For alkyl halides, the Hansch _et al_. (1968) correlation between S (molar) and partition coefficient (dimensionless) is:

$$\log P = 0.681 - 0.819 \log S.$$

The estimated value of P for bromoform is, therefore, 370. The partition coefficient, like the vapor pressure and solubility, appears to vary by no more than an order of magnitude for the chemicals under consideration. A value of 250 was selected as an estimate for $CHBrCl_2$ and $CHBr_2Cl$.

The Henry's Law constant listed in Table 3 is simply the ratio of the vapor pressure at 25°C to the water solubility (with no corrections for activity coefficients). This parameter is fundamentally related to the tendency of a solute to escape from water into the atmosphere. Once again, the range in values for chloroform and bromoform is not large. An average value of 2000 mm Hg - L/mole was assumed for $CHBr_2Cl$ and $CHBrCl_2$.

C. MONITORING DATA

1. Introduction

This section summarizes data regarding the presence of trihalomethane in the environmental media air, water, and biota. In general, limited data are available, especially for bromoform, bromodichloromethane, and dibromochloromethane, and no data were found regarding levels of trihalomethanes in soil. Levels of chloroform in POTW influent and effluent are discussed in Section IV.D.7.

2. Water

a. Seawater

The only monitoring data available for trihalomethanes in seawater were for chloroform. Pearson and McConnell (1975) found a maximum chloroform concentration of 1.0 ug/l in Liverpool Bay, U.K. Su and Goldberg (1976) found mean levels of 0.05 ug/l in open waters of the East Pacific, and average concentrations of 0.009-0.012 ug/l closer to shore. Murray and Riley (1973) reported mean chloroform concentrations of 0.0008 ug/l in the Northeast Atlantic.

b. Freshwater

STORET data provided the most complete survey of ambient concentrations of trihalomethanes in surface waters of the U.S. However, the data are far from complete: only 168 unremarked[1] measurements have been reported for chloroform, the most commonly monitored trihalomethane.

Summaries of the STORET data concerning trihalomethanes are given in Tables 4-7. Most of the chloroform concentrations were between 1 ug/l and 10 ug/l, and only rarely did they exceed 100 ug/l. Most of the data for bromoform were remarked; almost all of these concentrations were between 1 ug/l and 10 ug/l as well. For bromodichloromethane, the majority of the measured concentrations fell between 0.1 ug/l and 1.0 ug/l, with the exception of the Pacific Northwest, for which the reported levels were approximately one order of magnitude higher. Two-thirds of

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[1] A large number of data entries for trihalomethanes in the STORET system are "remarked." This means that some note regarding the data has been entered. In general, the notation refers to a value less than the detection limit. Thus, there is a large amount of uncertainty associated with "remarked" data.

TABLE 4. CONCENTRATIONS OF TOTAL CHLOROFORM DETECTED IN SURFACE WATERS OF THE U.S., 1970-1979

River Basin	No Samples		Percentage of Observations at Concentration			
	U[1]	R[2]	0.1-1 ug/1	1-10 ug/1	10-100 ug/1	100-1,000 ug/1
New England		4	100	0	0	0
Mid Atlantic	59	8	18	67	15	0
Southeast	7	3	30	70	0	0
Great Lakes	20	16	47	39	14	0
Ohio	15	12	41	59	0	0
Tennessee	7		14	43	43	0
Upper Mississippi	22	4	23	27	46	4
Lower Mississippi	9	3	33	67	0	0
Souris and Red of North		1	100	0	0	0
Missouri		5	100	0	0	0
Arkansas and Red		2	100	0	0	0
Western Gulf	7	2	33	67	0	0
Rio Grande and Pecos		2	100	0	0	0
Upper Colorado			-	-	-	-
Lower Colorado		2	100	0	0	0
Great Basin		1	100	0	0	0
Pacific Northwest	7	24	19	81	0	0
California	15	11	92	8	0	0
Alaska			-	-	-	-
Hawaii			-	-	-	-
United States	168	100	39	49	12	<1

[1] Unremarked data.

[2] Remarked data.

Source: U.S. Environmental Protection Agency, STORET (1979)

TABLE 5. CONCENTRATIONS OF TOTAL BROMOFORM DETECTED IN SURFACE WATERS OF THE U.S., 1970-1979

River Basin	No Samples		Percentage of Observations at Concentration		
	U[1]	R[2]	0.1-1 ug/l	1-10 ug/l	10-100 ug/l
New England		4	0	100	0
Mid Atlantic	4	12	0	100	0
Southeast		4	0	100	0
Great Lakes		8	0	100	0
Ohio		18	0	100	0
Tennessee	1	1	0	50	50
Upper Mississippi		6	0	100	0
Lower Mississippi		4	0	100	0
Souris and Red of North		1	0	100	0
Missouri		6	0	100	0
Arkansas and Red		2	0	100	0
Western Gulf		4	0	75	25
Rio Grande and Pecos		2	0	100	0
Upper Colorado			-	-	-
Lower Colorado		2	0	100	0
Great Basin		1	0	100	0
Pacific Northwest		29	3	97	0
California	12	12	0	100	0
Alaska			-	-	-
Hawaii			-	-	-
United States	17	114	1	97	2

[1] Unremarked data.

[2] Remarked data.

Source: U.S. Environmental Protection Agency, STORET (1979)

TABLE 6. CONCENTRATIONS OF TOTAL BROMODICHLOROMETHANE DETECTED IN SURFACE WATERS OF THE U.S., 1970-1979

River Basin	No Samples		Percentage of Observations at Concentration		
	U[1]	R[2]	0.1-1 ug/l	1-10 ug/l	10-100 ug/l
New England		4	100	0	0
Mid Atlantic	4	16	60	35	5
Southeast		4	100	0	0
Great Lakes	1	7	88	0	12
Ohio	2	18	60	40	0
Tennessee	2	1	33	0	67
Upper Mississippi	2	6	75	25	0
Lower Mississippi	2	4	67	17	16
Souris and Red of North		1	100	0	0
Missouri		6	100	0	0
Arkansas and Red		2	100	0	0
Western Gulf		3	100	0	0
Rio Grande and Pecos		2	100	0	0
Upper Colorado			-	-	-
Lower Colorado		2	100	0	0
Great Basin		1	100	0	0
Pacific Northwest		29	14	86	0
California	12	12	100	0	0
Alaska			-	-	-
Hawaii			-	-	-
United States	25	118	66	31	3

[1] Unremarked data.

[2] Remarked data.

Source: U.S. Environmental Protection Agency, STORET (1979)

TABLE 7. CONCENTRATIONS OF TOTAL DIBROMOCHLORMETHANE DETECTED IN SURFACE WATERS OF THE U.S., 1970-1979

River Basin	No Samples		Percentage of Observations at Concentration	
	U[1]	R[2]	0.1-1.0 ug/l	1-10 ug/l
New England		4	100	0
Mid Atlantic	2	12	86	14
Southeast		4	100	0
Great Lakes	1	7	88	12
Ohio		18	67	33
Tennessee		1	100	0
Upper Mississippi		6	100	0
Lower Mississippi		4	100	0
Souris and Red of North		1	100	0
Missouri		6	100	0
Arkansas and Red		2	100	0
Western Gulf		3	100	0
Rio Grande and Pecos		2	100	0
Upper Colorado			-	-
Lower Colorado		2	100	0
Great Basin		1	100	0
Pacific Northwest		29	17	83
California	12	12	25	75
Alaska		1	100	0
Hawaii			-	-
United States	15	115	80	20

[1] Unremarked Data.

[2] Remarked Data.

Source: U.S. Environmental Protection Agency, STORET (1979)

the dibromochloromethane concentrations also fell between 0.1 ug/l and 1.0 ug/l, although for California and the Pacific Northwest concentrations were roughly one order of magnitude greater. The apparent higher levels of these two chemicals in the Pacific Northwest and California are probably due to a higher detection limit for data from these areas.

Chloroform is the only trihalomethane for which data were found on concentrations in precipitation. Pearson and McConnell (1975) reported maximum concentrations of 0.2 ug/l in rainfall near Runcorn, U.K. Su and Goldberg (1976) found a mean level of 17 ug/l in rainwater collected in Southern California. The same authors reported chloroform levels in snow collected in different parts of North America, ranging from 3 ug/l to 90 ug/l.

3. Sediment

The only information available on trihalomethane concentrations in sediment was from Pearson and McConnell (1975) who found maximum chloroform residues of 4 mg/kg in Liverpool Bay, U.K.

4. Aquatic Organisms

STORET data on trihalomethane residues in fish were limited. Only one unremarked measurement was reported for each of the four compounds. All four measurements were taken in the Pacific Northwest basin, and the concentrations reported all fell between 1 mg/kg and 10 mg/kg. The remarked data, however, indicated concentrations from 100 mg/kg up to 100 mg/kg for each of the compounds.

Chloroform is the only trihalomethane compound for which any detailed residue data were found. The data of Pearson and McConnell (1975) as shown in Table 8 include residue analyses for 21 species of marine finfish and shellfish, as well as plankton. The plankton had the lowest overall residue levels (0.02-5 ug/kg, wet weight); shellfish residues ranged from 2 ug/kg to 180 ug/kg. Residues in finfish were analyzed in flesh, liver, and gastrointestinal tract. Residues of up to 50 ug/kg were found in mackerel flesh; concentrations in liver and gastrointestinal tract were generally one-third to one-tenth of those found in flesh.

5. Air

Chloroform is the only trihalomethane compound for which data on concentrations in air were found. Harsch *et al*. (1977) have reported that continental background levels of chloroform in the atmosphere range between 0.04 ug/m^3 and 0.13 ug/m^3. Oceanic background levels, as reported in NAS (1978), are somewhat higher, with mean concentrations ranging from 0.13 ug/m^3 to 0.20 ug/m^3.

In the urban environment, ambient atmospheric levels of chloroform may be considerably higher as a result of anthropogenic sources. The data of Harsch *et al*. (1977) suggest that concentrations in city air are highly dependent upon automobile activity. Urban air (Pullman,

TABLE 8. CHLOROFORM RESIDUES DETECTED IN MARINE ORGANISMS

Organism	Chloroform Concentration (ug/kg wet weight)
Plankton	0.02-5
Mussel (*Mytilus edulis*)	3-10
Cockle (*Cerastoderma edule*)	4-150
Oyster (*Ostrea edulis*)	3
Whelk (*Buccinum undatum*)	10
Slipper limpet (*Crepidula fornicata*)	6
Crab (*Cancer pagurus*)	3-180
Shore crab (*Carcinus maenas*)	15
Hermit crab (*Eupagurus bernhardus*)	20-73
Sand shrimp (*Crangon crangon*)	45
Starfish (*Asterias rubens*)	13
Sunstar (*Solaster* sp.)	3
Sea urchin (*Echinus esculentus*)	2
Flounder (*Platychthys flesus*), flesh/liver	21/6
Mackerel (*Scomber scombrus*), flesh/liver	50/18
Dab (*Limanda limanda*), flesh	23
Plaice (*Pleuronectes platessa*), flesh	17
Sole (*Solea solea*), flesh/gastrointestinal tract	26/9
Red gurnard (*Aspitrigla cuculus*), flesh/gastrointestinal	21/2
Scad (*Trachurus trachurus*), flesh	48
Pout (*Trisopterus luscus*), flesh	15
Spurdog (*Squalus acanthias*), flesh	110

Source: Pearson and McConnell (1975)

Washington) in the early morning contained 0.04 ug/m^3 chloroform; in light traffic the level was 0.10 ug/m^3; and in heavy traffic with no breeze, the concentration rose to 0.44 ug/m^3. Chloroform levels in automobile exhaust varied between 0.32 ug/m^3 and 33 ug/m^3, depending on car model and year. (The car equipped with a catalytic converter emitted fumes with chloroform levels approximately two orders of magnitude lower than a car that lacked this device.) Lillian et al. (1975) found a wider range of urban ambient levels, ranging from <0.05 ug/m^3 to 74 ug/m^3; the maximum value was reported for Bayonne, N.J.

Pellizzari et al. (1979) have sampled four highly industrial areas for halogenated organic compounds. Chloroform was commonly found in these samples, although none of the other trihalomethanes was reported. Table 9 summarizes the results. It can be seen that chloroform levels in air were highly variable, with a maximum of 139 ug/m^3 reported in the New Jersey area.

Harsch and Rasmussen (1977) have conducted extensive monitoring in various indoor environments, particularly in commercial establishments. Concentrations ranged from 0.07 ug/m^3 in the dining area of a restaurant to 3.6 ug/m^3 in the aisle of a food store containing household cleaners. However, chloroform levels rarely exceeded 0.5 ug/m^3, and most concentrations were similar to tropospheric background levels.

However, Pellizzari et al. (1979) sampled basements of houses in the Old Love Canal area, and found levels of chloroform ranging from 0.46 ug/m^3 to 13.48 ug/m^3 in the seven samples taken. Upstairs in the same homes concentrations from trace levels to 15.3 ug/m^3 chloroform were found.

D. ENVIRONMENTAL PATHWAYS AND FATE

1. Overview

This section examines the sources of trihalomethanes released to the environment, as discussed in Chapter III, the chemistry of their inadvertent production, and the fate of these chemicals in various environmental compartments. Most of this discussion is centered around chloroform, but the general fate of the other trihalomethanes is expected to be similar.

2. Sources to the Environment

The largest of the identified sources of chloroform released to the environment are pulp and paper bleaching, the chlorination of drinking water and wastewater, and the use of this chemical in pharmaceutical extractions. The greater portion of these releases goes to air (~17,000 kkg/yr), while about 900 kkg/yr are released to water. Figure 4 shows a general representation of the releases of chloroform, as well as their ultimate distribution in the environment.

TABLE 9. CHLOROFORM CONCENTRATIONS DETECTED IN AMBIENT AIR OF INDUSTRIAL AREAS

City	Concentration (ug/m^3) Mean	Range	No. Detected/No. Samples
Niagara Falls and Buffalo, N.Y.	89,000	1050-105,461	9/9
Rahway/Woodbridge, Boundbrook and Passaic, N.J.	47,000	T[1] - 98,625	75/93
Baton Rouge, Geismar, and Plaquemine, LA	5,500	181-11,742	78/87
Houston, Deer Park and Pasadena, TX	1,000	T - 53,846	29/30

[1] Trace

Source: Pellizzari *et al*. (1979)

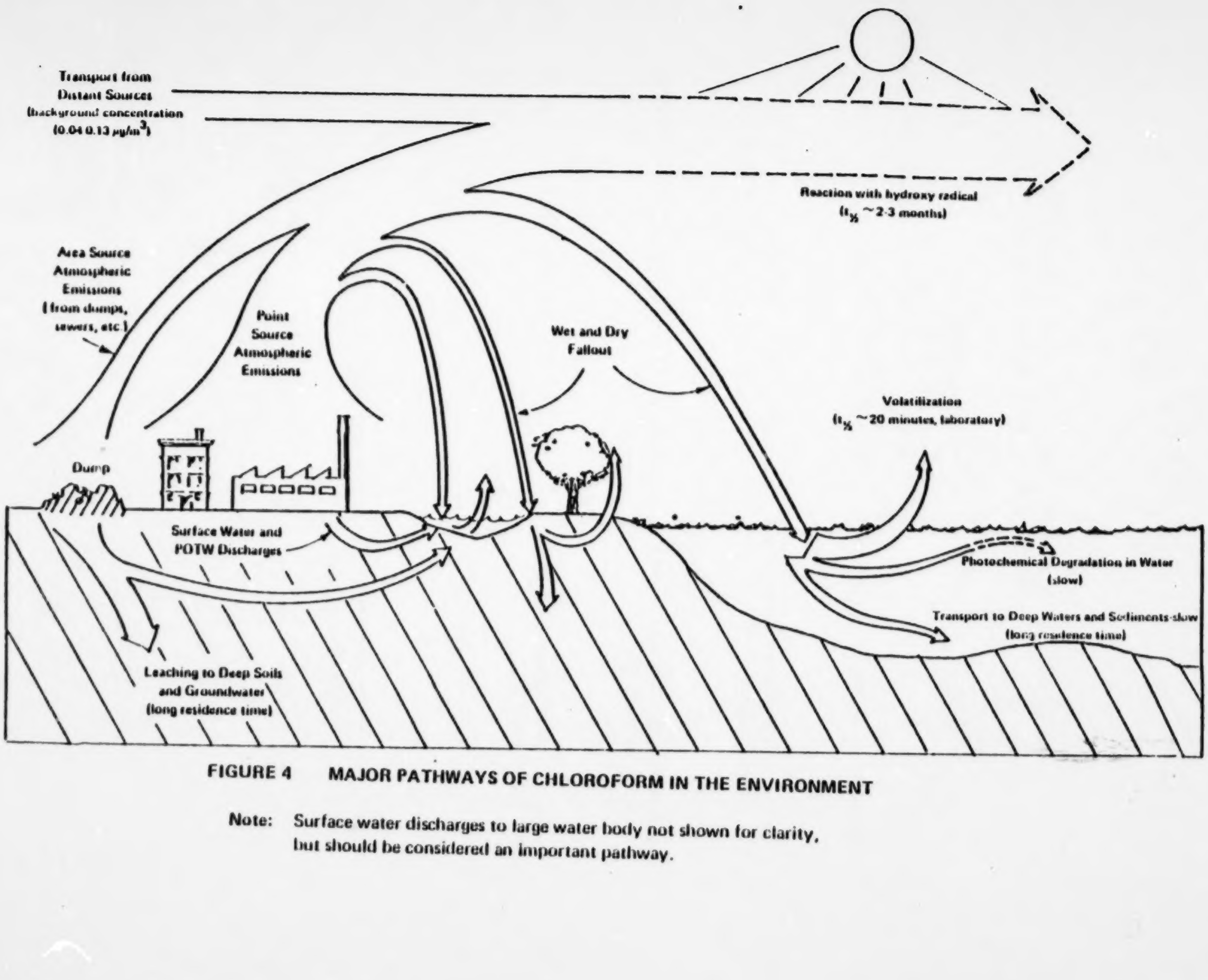

Transport from
Distant Sources
(background concentration
(0.04-0.13 μg/m³)
Reaction with hydroxy radical
($t_{1/2}$ ~2-3 months)
Area Source
Atmospheric
Emissions
(from dumps,
sewers, etc.)
Point
Source
Atmospheric
Emissions
Wet and Dry
Fallout
Volatilization
($t_{1/2}$ ~20 minutes, laboratory)
Dump
Surface Water and
POTW Discharges
Photochemical Degradation in Water
(slow)
Transport to Deep Waters and Sediments-slow
(long residence time)
Leaching to Deep Soils
and Groundwater
(long residence time)

FIGURE 4 MAJOR PATHWAYS OF CHLOROFORM IN THE ENVIRONMENT

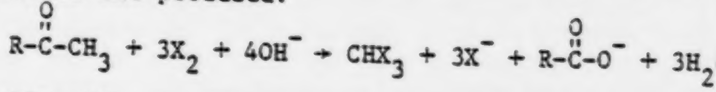
Note: Surface water discharges to large water body not shown for clarity, but should be considered an important pathway.

3. Inadvertent Formation of Trihalomethanes

Since the formation of trihalomethanes upon chlorination has been shown to be an important source of these chemicals in the environment, it is important to consider the chemistry of these reactions.

Fulvic and humic acids constitute the major portion of the organic matter in surface or ground waters and have been demonstrated to be precursors for haloforms when treated with chlorine (Rook 1974). The reactions cited are direct analogs to the haloform reaction; these reactions are initiated by the hypochlorite ion present in chlorinated waters.

One suggested mechanism for trihalomethane formation during industrial bleaching and water purification processes is given in reaction 1 (Hendrickson _et al_. 1970). This reaction is a direct analog of the haloform reaction and is seen with methyl ketones ($-\overset{O}{\overset{\|}{C}}-CH_3$) or compounds that can be readily oxidized to produce methyl ketones. The reaction is base catalyzed; since each halogen introduced increases the acidity of the remaining hydrogens, the intermediates are unstable and trihalomethanes are produced.

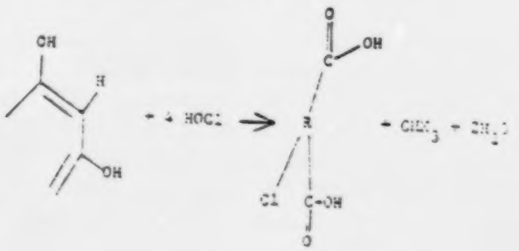


$$R-\overset{O}{\overset{\|}{C}}-CH_3 + 3X_2 + 4OH^- \rightarrow CHX_3 + 3X^- + R-\overset{O}{\overset{\|}{C}}-O^- + 3H_2O \qquad (1)$$

where X = Cl and/or Br (Hendrickson _et al_. 1970)

The presence of bromide ion in aqueous systems has been shown to reduce substantially the yield of chloroform, while increasing levels of dichlorobromomethane, bromodichloromethane, and bromoform (Bunn _et al_. 1975). Available hypochlorite ion oxidizes bromide to give bromine, which then undergoes the "haloform" type reaction to form the appropriate bromochloromethanes as shown in reaction 1.

The above mechanism is certainly applicable to industrial chlorination processes; however, the pH range of municipal water chlorination is much closer to neutral. For this reason, and the observation that a variety of degradation products other than trihalomethanes were produced in nonbasic aqueous solutions, a mechanism other than the base-catalyzed halogenation was suspected. For chlorination in aqueous solutions, Rook (1977) proposes a slightly different pathway and has determined that the most reactive site for the haloform reaction with fulvic acids at neutral pH is at the carbon between two meta-OH groups. His mechanism is outlined in reaction 2. The incorporation of bromine is according to the pathway outlined above.



(Rook 1977) (2)

4. Fate in the Atmospheric Environment

Versar (1979a,b) has concluded on the basis of a review of the literature that once chloroform is in the troposphere, reaction with hydroxyl radicals is the primary mechanism for removal. They reported, based upon the work of Spence et al. (1976), Hanst (1978), and the U.S. EPA (1975), that the product of this reaction is a CCl_3 radical, which is oxidized to produce phosgene ($COCl_2$) and chlorine oxide (ClO). The estimated lifetime is reported to be 2-3 months, based on reported lifetimes of 0.19 years and 0.32 years reported by Cox et al. (1976) and Yung et al. (1975). Bromo-alkanes generally have rate constants for reaction with hydroxyl radical that are the same or slightly higher than those for the chlorinated analogs. Thus, the atmospheric residence times of $CHBrCl_2$, $CHBr_2Cl$ and $CHBr_3$ are also expected to be on the order of 2 to 3 months.

Direct photochemical degradation of trihalomethanes in the troposphere is not likely to be important because these species do not absorb UV radiation at wavelengths that penetrate the ozone layer. The estimated atmospheric residence time is sufficiently short that extensive transport to the stratosphere, where direct photochemical process could occur, may not be a major pathway. Export from the atmosphere by rainout is a possible, but not probable fate. The magnitude of the vapor pressure in comparison with the solubility suggests that an insignificant fraction of chloroform in the atmosphere would be associated with water droplets or dust particles. Since the other trihalomethanes have similar Henry's Law constants, they also are expected to be resistant to rainout.

Thus, trihalomethanes reaching the atmosphere may travel considerable distances before reaction with the hydroxyl radical results in degradation.

5. Fate in the Aquatic Environment

Of the numerous modes by which the trihalomethanes might be removed from the aquatic environment, volatilization is expected to be the most significant. A laboratory study by Dilling et al. (1975) indicated that the half-life for evaporation of chloroform from a stirred aqueous solution was about 20 minutes, compared with a 1-minute prediction based on vapor pressure and solubility. In fact, the results obtained strongly suggest that the mass transport phenomena were limiting the evaporation rate, since the same half-life (20 minutes) was observed for several alkylhalides with vapor pressures from 19 mm to 426 mm.

The rate constants for hydrolysis of the bromo/chloro trihalomethanes, as compiled by Mabey and Mill (1977), are summarized in Table 10. The reactions are base catalyzed, but the rate constants for the basic hydrolysis are not high enough to decrease significantly the predicted hydrolytic half-life within the normal environmental pH range (pH 5-8 for most natural waters). Chloroform, for example, has a predicted half-life of $\geq$500 days at pH 7 due to neutral hydrolysis, while the basic

TABLE 10. RATE CONSTANTS FOR HYDROLYSIS OF TRIHALOMETHANES

Compound	Temp. (°C)	Rate Constant: Neutral $10^8k_n\mathrm{sec}^{-1}$	Rate Constant: Basic $10^4k_{OH}M^{-1}\mathrm{sec}^{-1}$
Chloroform	25	1.62[1]	
	100	7.29	
	25		0.60
Bromodichloromethane	25		16.0
Dibromochloromethane	25		8.01
Bromoform	25		3.20

[1] Considered to be "suspect" value by Mabey and Mill (1977) because of poor temperature control during measurement. If the 100°C value is considered to be reliable, a 25° value much lower than 1.62 (ca 0.07 perhaps) would be more likely for a reaction with a typical activation energy.

Source: Mabey and Mill (1977)

hydrolysis reaction at pH 8 would give a 500-year half-life. The base-catalyzed reaction rate constants of Table 10 are included because they provide one indication of the relative reactivity of the trihalomethanes. With regard to basic hydrolysis, the relative reactivities are: chloroform (1), bromoform (5), dibromochloromethane (13), bromodichloromethane (27). It is not clear that the same order of magnitude would be observed for the neutral reactions, because the reaction mechanism may be significantly different. However, it appears probable that the mixed trihalomethanes have considerably shorter hydrolytic half-lives than bromoform or chloroform. It also appears likely that hydrolysis is not fast enough under any conditions to compete with volatilization as a pathway for loss from the aquatic compartment.

The octanol/water partition coefficient of 90 suggests that a significant portion of chloroform in the hydrosphere is associated with suspended solids and sediments (Lyman 1978). However, there is no experimental evidence to support this as an important pathway, and no monitoring data exist for chloroform in sediment. Thus, it is not clear that adsorption competes with volatilization as an important fate pathway.

Similarly, no information is available regarding the biodegradation of trihalomethane in aqueous systems. However, again it is unlikely that this mechanism could compete with volatilization.

Bioaccumulation does not appear to represent an important fate pathway, although the octanol-water partition coefficient of 90 suggests that accumulation may occur. In a summary of bioaccumulation studies on various aquatic animals, U.S. EPA (1978) found a mean bioconcentration factor of 6, following 14 days of exposure to a 110 ug/l solution of chloroform. The half-life of chloroform in the tissues was found to be less than 24 hours. Preliminary accumulation tests on channel catfish by Anderson et al. (1979) indicated a bioconcentration factor of approximately 10 over ambient water levels, with the chloroform levels in fat, eggs, and gastrointestinal system at least twice those of levels in other tissues.

Anderson et al. (1979) also conducted a 28-day uptake/28-day depuration study of bromoform, using menhaden, oysters, shrimp, and two species of clams (all marine species). After 24 hours of exposure to bromoform, all species were found to have bromoform residues in the tissues, and within a 48-hour depuration period bromoform residues disappeared. In the highest bromoform concentrations (0.21 mg/l to 19 mg/l, depending on the species), tissue levels were usually lower than those in the water; in low concentrations (0.03 mg/l) the reverse was true.

6. Fate in Soil and Sediment

Little is known regarding the fate of trihalomethanes in soils and sediment. Volatilization is likely from surface soils, and is probably the dominant pathway. However, some movement may occur, as evidenced by some detectable levels of chloroform in ground waters (Coniglio _et al_. 1979).

Lyman (1978) suggests that some chemical degradation may occur. Adsorption is also not likely to be important because of the high solubility and vapor pressure of the trihalomethanes. The importance of biodegradation is unknown.

One recent study by Wilson _et al_. (1980) investigated the fate of chloroform and dichlorobromomethane in a sandy soil. In a soil column receiving solutions of these chemicals, most was volatilized (66-122%) and 31-48% was recovered in the column effluent. Actually, more was recovered than applied. This excess was attributed to an overestimation of the amounts volatilized. Degradation in the column was thought to be insignificant. These authors calculated retardation factors, which represent the interstitial water velocity/velocity of the pollutant. The finding that these factors were less than 1.5 for both chemicals suggests that little adsorption was occurring.

Thus, trihalomethanes are likely to be volatilized from surface soils. Otherwise, they are subject to migration into aquifers.

7. Fate in Water Distribution Systems

Because of the importance of the chlorination process in trihalomethane formation, some consideration was given to the fate of trihalomethanes in water distribution systems. An EPA study of the sources of priority pollutants found in publicly owned treatment works provides a means of estimating the extent of loss and regeneration of trihalomethanes in aqueous solutions (Levins _et al_.. 1979a). Samples were collected at the POTW, as well as at various source locations (residential, commercial, and industrial). The summary data from four separate studies are presented in Table 11. The concentrations of the trihalomethanes were consistently higher in the samples of tap water than in the POTW influent samples, indicating either dilution or volatilization is occurring. The relative proportions of the concentrations of the four trihalomethanes are fairly consistent from the tap to the sewers to the influent. Data for bromoform are inconclusive because of the very low concentrations reported. The data indicate that the rates of dilution or volatilization are similar for the four compounds. They also suggest that levels of these compounds are not being augmented by mechanisms other than chlorination. The sources sampled in this study did not include any paper and pulp industries.

Table 12 presents the mass flows for one city (Levins _et al_. 1979b). It can be seen that significant percentages of the trihalomethanes produced on chlorination are lost between the tap and the influent, either through volatilization or consumptive use of tap water. Furthermore, a comparison of the sum of the mass flows for each of the scaled-up source categories with the mass flow at the influent shows that very little loss takes place within the sewer system.

TABLE 11. TRIHALOMETHANE CONCENTRATIONS AT VARIOUS LOCATIONS IN POTW SYSTEMS (averaged for four cities)

	Location									
	Tap Water		Sewers Serving Residential areas		Sewers Serving Commercial areas		Sewers Serving Industrial areas		Influent to POTW	
Compound	Det. Freq. (%)	Mean Conc. (ug/1)	Det. Freq. (%)	Mean Conc. (ug/1)	Det. Freq. (%)	Mean Conc. (ug/1)	Det. Freq. (%)	Mean Conc. (ug/1)	Det. Freq. (%)	Mean Conc. (ug/1)
Chloroform	100	27	91	3	100	7	100	12	100	5
Bromodichloromethane	100	9	4	-	50	1	57	2	11	0.2
Bromoform	33	0.8	-	-	-	-	-	-	-	-
Dibromochloromethane	58	6	4	-	43	0.7	57	1	22	0.2

Source: Levins *et al*. (1979a)

TABLE 12. MASS FLOW ANALYSIS OF POTW DATA FOR TRIHALOMETHANES

	Mass Flow[1] (kg/day)				
Compound	Tap Water[2]	Known Sources to POTW[3]	Influent to POTW[4]	Influent/Sum	Tap/Influent
Chloroform	1.85	0.45	0.54	1.2	3.4
Bromodichloromethane	1.10	0.06	0.06	1.0	18.3
Dibromochloromethane	0.71	0.04	0.09	2.2	7.9

[1] Calculated by use of the assumption that tap flow equals influent flow.

[2] Flow of trihalomethanes at the tap.

[3] Sum of all mass flows to POTW.

[4] Measure of mass flow at influent to POTW.

Source: Levins *et al*. (1979b)

E. MODELING OF CHLOROFORM IN THE ENVIRONMENT

1. Estimated Environmental Distribution

A preliminary estimate of the environmental distribution of the bromo/chloro trihalomethanes was attempted by application of the simple model of Neely (1978). Neely's model consists of regression equations that correlate the percentage distribution of a chemical among air, water, and soil compartments with the Henry's Law constant and the aqueous solubility. These equations predict that, at equilibrium, all of the halomethanes under consideration would be almost entirely in the air compartment, with 1% or less in either the water or soil compartments. It is important to note, however, that the equilibrium distribution among phases may not be attained in an actual situation. For volatile species such as trihalomethanes, the intercompartmental distribution is affected by kinetic, as well as thermodynamic, factors.

The probable distribution of the residual amounts of trihalomethanes between water and soil/sediment within the aqueous compartment can be predicted from the soil adsorption models developed at the U.S. EPA Athens laboratory (Means et al. 1978, Karickhoff et al. 1979). This suggests that the ratio of sediment concentration to water concentration is related to the water-octanol partition coefficient:

$$\frac{C_{sediment}}{C_{water}} = \frac{P}{1.62} \times \text{organic content of sediment}$$

For a typical river sediment containing 2% organic carbon or less, the sediment to water concentration ratio for the halomethanes ranges from about 1 (chloroform) to about 5 (bromoform). Trace amounts of trihalomethanes that have not (yet) volatilized may thus be expected to be found in both soil and aqueous phases.

2. EXAMS Model Results

For the purpose of examining the probable fate of chloroform in various aquatic environments under conditions of continuous discharge, the EXAMS (Exposure Assessment Modelling System; U.S. EPA-SERL, Athens, Ga.) model AETOX 1 was implemented.

Rate constants for the primary processes thought to influence the fate of chloroform in aqueous environments were estimated (SRI 1980) and are presented in Table 13.

A loading rate for trichloromethane was estimated using the following assumptions for a pulping plant: 0.1 lb trichloromethane discharged per ton of pulp production, 500 tons of production per day, therefore, 2 lbs or 1 kg trichloromethane released per hour (JRB Associates 1980 and Andrew Caren, NCASI, personal communication 1980). This estimate is not meant to be representative of the industry but to provide a reasonable example of a discharge rate.)

TABLE 13. RATE CONSTANTS USED IN EXAMS ANALYSIS OF THE AQUATIC FATE OF CHLOROFORM

Process	Rate Constant	Units
Volatilization	0.583	dimensionless
Hydrolysis (base-catalyzed)	0.23	mole $[OH^-]^{-1}$ hr^{-1}
Hydrolysis (neutral)	5.40×10^{-9}	hr^{-1}
Oxidation (water column)	0.70	mole $(oxidants)^{-1}$ hr^{-1}
Oxidation (sediment)	360.0	mole $(oxidants)^{-1}$ hr^{-1}

Source: SRI (1980)

Six prototype systems were simulated in order to provide a range of environmental conditions: pond, eutrophic and oligotrophic lakes, and three river systems (average, turbid, and coastal plain).

As would be expected, in relatively static systems (pond and lakes) in which physical transport processes did not dominate, volatilization was the most important removal mechanism, responsible for a 93-96% loss of the equilibrium chloroform mass. Table 14 presents information on the distribution and transformation of chloroform in the different systems. In all the river systems (1-km segments), transport downstream alone accounted for at least 85% of the removal, and at a much faster rate than volatilization (on the order of hours rather than days). The overall time for self-purification (following cessation of discharge) was thus over 2 months for the lakes, approximately 1 month for the pond, and less than 2 days for the rivers.

Table 15 presents the simulated chloroform concentrations in different environmental compartments (water column, sediment, plankton and benthos) at steady-state conditions. Water concentrations were approximately 0.1-3 mg/l in the pond and lake systems and considerably lower (due to dilution and flow rates), 1-10 ug/l, in the river systems. Sediment concentrations were variable, ranging from ~0.8 ug/kg up to about 8 mg/kg. The highest levels were reached in the pond, where the rates of both volatilization and physical transport were not fast enough to prevent accumulation slightly above water column concentrations. Concentrations in biota were generally one to two orders of magnitude above levels in water.

Based on the results of the EXAMS run and dependent on the assumptions of the model and the rate constants used as input, some conclusions can be drawn about the potential environmental behavior of chloroform. In relatively static systems with slow flow rates (e.g. lakes), persistence is a function of volatilization. In more dynamic river systems, physical transport processes are much more competitive for chloroform, removing it before volatilization can reduce the mass significantly. Transformation processes and bioaccumulation will not significantly reduce water concentrations. The sediment layer does not appear to absorb chloroform at levels much above water concentrations; in fact, these levels are sometimes lower than water levels. Since volatilization is such an important parameter, then the environmental factors that increase volatilization rates -- conditions of high temperature, high wind speeds, turbulence of the water, and others -- would increase the rate of loss of chloroform.

Figure 5 further illustrates the difference between a static system's (eutrophic lake) and a dynamic system's (river) response following the termination of a chloroform discharge (after a system equilibrium has been reached). Within the 12 hours following the last discharge, there is little change in chloroform concentration that is primarily controlled by volatilization. In the river system, however, physical transport processes reduce the concentration significantly by five orders of

TABLE 14. THE FATE OF CHLOROFORM IN VARIOUS GENERALIZED AQUATIC SYSTEMS[1]

System	Percent Distribution		Percent Lost by Various Processes				
	Residing in Water at Steady-State 1	Residing in Sediment at Steady-State	Transformed by Chemical Processes	Transformed by Biological Processes	Volatilized	Lost by Other Processes[2]	Time for System Self-Purification[3]
Pond	90.53	9.47	0	0	93.35	6.65	888.4 hr
Eutrophic Lake	99.93	0.07	0	0	96.14	3.86	56.31 days
Oligotrophic Lake	99.99	0.01	0	0	95.62	4.38	66.26 days
River	99.01	0.99	0	0	1.74	98.26	15.71 hr
Tubid River	99.30	0.70	0	0	1.74	98.26	11.25 hr
Coastal Plain	98.01	1.99	0	0	15.36	84.64	57.77 hr

[1] All data simulated by the EXAMS (U.S. EPA-SERL, Athens, Ga.) model (see text for further information).

[2] Including loss through physical transport out of system.

[3] Estimate for removal of ca. 75% of the toxicant accumulated in system. Estimated from the results of the half-lives for the toxicant in bottom sediment and water columns, with overall cleansing time weighted according to the pollutant's initial distribution.

TABLE 15. STEADY-STATE CONCENTRATIONS OF CHLOROFORM IN VARIOUS GENERALIZED AQUATIC SYSTEMS RESULTING FROM CONTINUOUS DISCHARGE AT RATE OF 1.0 kg/hr[1]

		Maximum Concentrations							
System	Loading	Water Dissolved (mg/l)	Water Total (mg/l)	Bottom Sediment (mg/l)	Maximum in Sediment Deposits (mg/l)	Plankton (ug/g)	Benthos (ug/g)	Total Steady-State Accumulation (kg)	Total Daily Load (kg/day)
Pond	1.0 kg hr^{-1}	2.5	2.5	1.4	7.7	38	22	55	24
Eutrophic Lake	"	0.13	0.13	5.1×10^{-3}	1.2×10^{-2}	1.9	7.9×10^{-2}	300	24
Oligotrophic Lake	"	0.13	0.13	1.7×10^{-3}	4.1×10^{-3}	2.0	2.6×10^{-2}	340	24
River	"	9.9×10^{-4}	9.9×10^{-4}	3.0×10^{-4}	1.1×10^{-3}	1.5×10^{-2}	4.7×10^{-3}	0.90	24
Turbid River	"	9.9×10^{-4}	9.9×10^{-4}	6.3×10^{-4}	8.6×10^{-4}	1.5×10^{-2}	9.6×10^{-3}	0.89	24
Coastal Plain River	"	9.3×10^{-3}	9.3×10^{-3}	3.0×10^{-3}	1.6×10^{-2}	0.14	4.6×10^{-2}	8.0	24

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[1] All data simulated by EXAMS (U.S. EPA-SERL, Athens, Ga.) model (see text for further information).

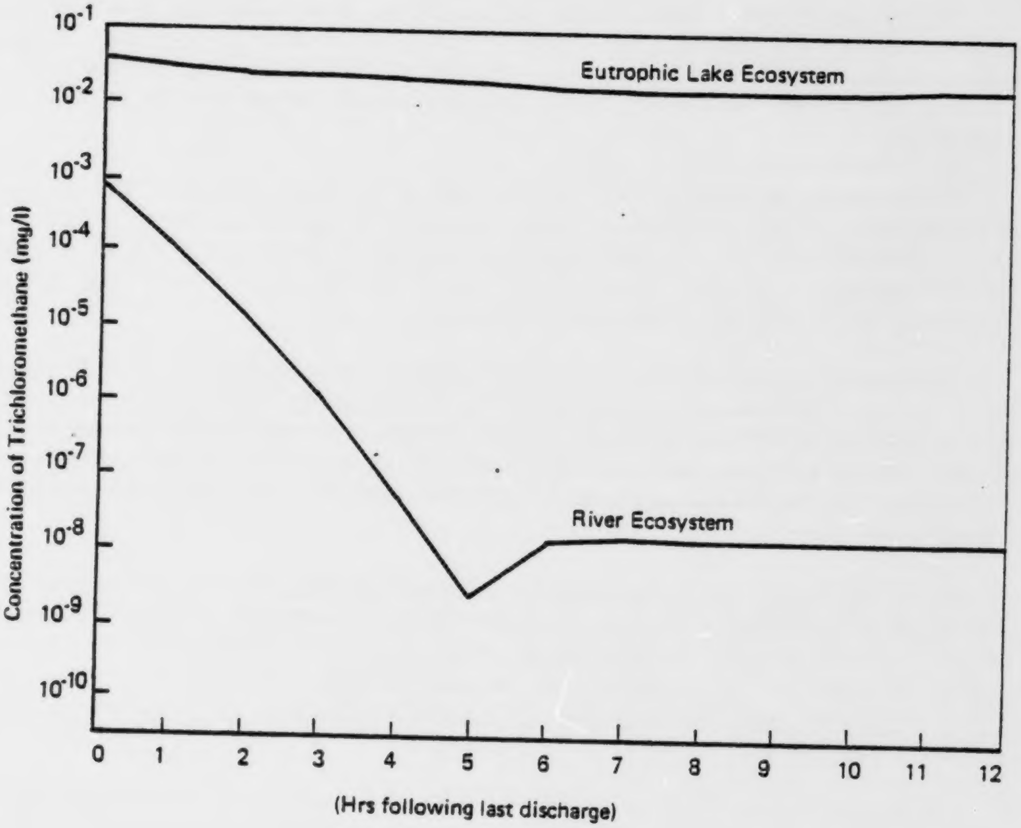

FIGURE 5 CONCENTRATION OF TRICHLOROMETHANE IN WATER COLUMN FOLLOWING CESSATION OF DISCHARGE AT 1.0 KG HR^{-1}

magnitude, in the first 5 hours. Although the rate of removal by physical transport is almost entirely system dependent (e.g. dependent on flow rate, etc.), one can assume that through many systems most of the chloroform would be removed from the vicinity of discharge before significant volatilization occurs.

F. SUMMARY

Trihalomethanes, especially chloroform, are commonly found in the natural waters of the United States. Levels in the open ocean appear to be in the range of 1-10 ug/l. The other trihalomethanes are not commonly detected, and when found are at lower concentrations than chloroform.

Chloroform is also found in ambient air, both indoors and outdoors. Continental background levels range from 0.04 ug/m^3 to 0.13 ug/m^3, while marine background levels are somewhat higher. Levels in urban areas are highly variable, ranging from <0.05 ug/m^3 to 90 ug/m^3, with the maximum occurring in a highly industrialized area.

The fate of trihalomethanes is largely controlled by their volatility. While much of the chloroform is originally released to the air, that reaching water is rapidly volatilized. The half-life of volatilization from a stirred aqueous solution is 20 minutes. The importance of hydrolysis, adsorption and biodegradation appear low compared with volatilization.

Once reaching the atmosphere, chloroform and the other trihalomethanes as well, probably travel considerable distances before degradation occurs. The lifetime in the troposphere has been estimated to be 2-3 months, attributable primarily to reaction with hydroxyl radicals. Direct photochemical degradation of trihalomethane, as well as rainout, are not expected to be important pathways.

Volatilization is also likely from soil surfaces. Biodegradation and adsorption are not likely to be important fate processes. Thus, trihalomethanes that are not volatilized are subject to rapid movement downward.

A partitioning model suggests that at equilibrium, all of the trihalomethanes would be primarily (>99%) in the air compartment. EXAMS also showed that volatilization was the dominant fate process in lakes and ponds. In rivers, physical transport over the short stretch of river modelled dominated volatilization.

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CHAPTER V

EFFECTS AND EXPOSURE -- HUMANS

A. HUMAN TOXICITY

1. Chloroform

a. Introduction

Prior to the mid-1940s, chloroform was widely used as an anesthetic and, until recently, was utilized in many pharmaceutical preparations (e.g., cough medicine, mouthwashes, dentifrices, linaments). The possibility of chloroform carcinogenicity in rodents has raised concern about long-term, low level exposure in man, particularly in view of recent findings of chloroform in concentrations up to 300 ug/l in the drinking water of municipalities throughout the United States. This section of the report examines the extensive data base on the toxic effects of chloroform in man and laboratory animals.

b. Metabolism and Bioaccumulation

Chloroform ($CHCl_3$) is rapidly absorbed through the lungs, through the gastrointestinal tract if ingested, and, to a lesser extent, through intact skin (Brown et al. 1974, Van Dyke et al. 1964). With some species variation, chloroform is partially excreted unchanged and partially metabolized to carbon dioxide (CO_2) and unidentified urinary metabolites in mice, rats, monkeys, and humans (NAS 1977). Pohl et al. (1977) recently reported that chloroform was metabolically activated to phosgene ($COCl_2$) by liver microsomes of phenobarbital-pretreated rats.

Mice exhibit the highest conversion rate to CO_2, metabolizing approximately 80% of a 60-mg/kg oral dose of $^{14}CO_2$ (Brown et al. 1974). No differences in the conversion rate due to strain (Brown et al. 1974) or sex (Taylor et al. 1974) were noted. Tissue distribution of the radio-label, however, showed striking sex differences: males had higher levels of radioactivity (∿ threefold) bound to the renal cortex and medulla, while females accumulated the label in the liver to a greater extent than males (Taylor et al. 1974).

In rats administered 60 mg/kg $^{14}CHCl_3$ by gavage, 66% of the dose was metabolized to $^{14}CO_2$, with an additional 20% of the dose eliminated unchanged in expired air (Brown et al. 1974). Administration of a much larger dose (1,484 mg/kg) intraduodenally resulted in a much smaller conversion to CO_2 (4%); the major portion of the dose (70%) was eliminated unchanged in expired air (Van Dyke et al. 1964).

Only 17% of an orally administered dose of $^{14}CHCl_3$ (60 mg/kg) was metabolized to $^{14}CO_2$ in the squirrel monkey; 78% of the dose was excreted unchanged in expired air (Brown et al. 1974).

In eight healthy human volunteers, between 17.8% and 66.6% of unchanged chloroform was recovered in expired air within an 8-hour-period following oral administration of a gelatin capsule containing 500 mg of chloroform (∿ 7 mg/kg) in olive oil. The wide range of values is partially attributable to body weight variations (58-80 kg); obese subjects excreted a smaller proportion of the dose through the lungs as unchanged chloroform. The maximum pulmonary excretion occurred between 40 and 120 minutes post-dosing. Less than 1% of the dose was detected in urine (Fry et al. 1972). In a separate experiment, two subjects, one male and one female, swallowed a capsule containing 500 mg of ^{13}C-labelled chloroform. A total of 50.6% and 48.5% of the dose was accounted for as exhaled $^{13}CO_2$ for the male and female subject, respectively (Fry et al. 1972).

Poobalsingham and Payne (1978) studied the rate of alveolar uptake of chloroform in 16 patients undergoing elective surgery. Eight patients spontaneously breathed known concentrations (2-2.5%) of chloroform; the second group were artificially ventilated with a fixed inspired concentration of 1% chloroform. Initial uptake of chloroform was rapid in both groups, approaching a plateau after 40-45 minutes. Expressed as a percentage of the equilibrium value, the arterial concentration of chloroform increased more steeply with controlled ventilation than with spontaneous breathing. In spontaneously breathing patients, the arterial concentration reached approximately 25% of the inspired concentration after about 1 hour of exposure compared with an equilibration of approximately 41% in the same time period under controlled ventilation. Increasing concentrations of chloroform in the blood of spontaneously breathing patients causes respiratory depression sufficient to reduce alveolar ventilation. Elimination following chloroform withdrawal was rapid and exponential in nature.

An average chloroform concentration of 51 ug/kg (range: 5-68 ug/kg wet tissue) was detected in postmortem samples of body fat taken from eight subjects between 48 and 82 years of age. Concentrations of 1.0 ug/kg to 10 ug/kg were present in kidney, liver, and brain tissues (McConnell et al. 1975).

In summation, chloroform is rapidly absorbed from the lungs and gastrointestinal tract, and to a lesser extent, through intact skin. With some species differences, chloroform is excreted partially unchanged and partially metabolized to CO_2 and unidentified urinary metabolites. Body organs contain 1-10 ug/kg, with 5-68 ug/kg chloroform detected in body fat.

c. Animal Studies

i. Carcinogenesis

Chloroform was implicated as a possible carcinogen more than 30 years ago by Eschenbrenner and Miller (1945). They administered 30 oral doses of 0, 150, 300, 600, 1200 or 2400 mg/kg chloroform to groups of five male and female strain A mice at 4-day intervals. Males in the three highest treatment groups and females receiving 2400 mg/kg chloroform died within 48 hours. When the mice were 8 months of age, nonmetastasizing hepatomas and cirrhosis were found in all surviving females given 600 mg/kg or 1200 mg/kg. No hepatomas were seen in either male or female mice at the lower dosage levels.

An abstract of another study of limited duration reports that Rudall (1967) gave 24 mice (strain unspecified) 0.1 ml or a 40% solution of chloroform orally twice weekly for 6 months. Three hepatomas were found in the five survivors. No additional information was given.

USP-grade chloroform in corn oil was administered by gavage to groups of 50 male and female mice (B6C3F1 strain) at a predetermined maximally tolerated dose and one-half this amount 5 days per week for 78 weeks. The dose of chloroform was changed during the course of the experiment; time-weighted-average doses were 138 mg/kg and 277 mg/kg for males and 238 mg/kg and 477 mg/kg for females. The vehicle control group consisted of 20 mice of each sex.

Frank hepatocellular carcinoma was found in 36% to 98% of treated mice ($p<0.001$) compared with 0% to 6% incidence in controls (see Table 16). Nodular hyperplasia of the liver was observed in several low-dose males that had not developed hepatocellular carcinoma (NCI 1976, Powers and Voelker 1976, Renne et al. 1976).

A concurrent study was conducted with groups of 50, 52-day-old Osborne-Mendel rats given time-weighted oral doses of 90 mg/kg and 180 mg/kg chloroform for males and 100 mg/kg and 200 mg/kg for females for 78 weeks. A significant ($p=0.0016$) increase in the incidence of kidney epithelial tumors was seen in males: 8% at 90 mg/kg; 24% at 180 mg/kg compared with none in controls. An increase in thyroid tumors was observed in female rats, but was not considered as resulting from the chloroform exposure (NCI 1976, Renne et al. 1976).

Another recent series of studies (Roe et al. 1979, Palmer et al. 1979, Heywood et al. 1979) examined the carcinogenic effects of feeding chloroform to Sprague-Dawley rats, beagles, and four strains of mice at dosage levels ranging from 15 mg/kg to 60 mg/kg. Except for an excess of renal tumors in male ICI/CFLP mice at the 60-mg/kg treatment level, no carcinogenic effects were reported.

In the first study, four strains of mice (male and female ICI/CFLP, male C57B6, CF/1 and CBA) were administered chloroform in a toothpaste

TABLE 16. INCIDENCE OF HEPATOCELLULAR CARCINOMA IN B6C3F1 MICE EXPOSED TO CHLOROFORM

Experimental Group	No. Mice with Carcinoma (% incidence)			
	Male		Female	
High $CHCl_3$ Dose	44/45	(98)	39/41	(95)
Low $CHCl_3$ Dose	18/50	(36)	36/45	(80)
Control	1/18	(6)	0/20	(0)

Source: NCI (1976), Powers and Voelker (1976), Renne *et al*. (1976)

TABLE 17. DISTRIBUTION OF NODULES AND FATTY CYSTS IN THE LIVERS OF CHLOROFORM-TREATED BEAGLE DOGS

Treatment Group	No. Dogs with Nodules (% incidence)		No. Dogs with Fatty Cysts (% incidence)	
	Male	Female	Male	Female
30 mg $CHCl_3$/kg/day	0/7 (0)	4/8 (50)	7/7 (100)	7/8 (88)
15 mg $CHCl_3$/kg/day	1/7 (14)	1/8 (13)	6/7 (86)	5/8 (63
vehicle control	0/15 (0)	3/12 (25)	8/15 (53)	3/12 (25)
untreated control	1/7 (14)	1/5 (20)	2/7 (29)	1/5 (20)

Source: Heywood *et al*. (1979)

vehicle by gavage 6 days per week for 80 weeks, followed by 16-24 weeks of observation. No overall increase in neoplastic changes was observed, except for an increase in tumors of the renal cortex in male ICI/CFLP mice (9/52) at the 60-mg/kg level compared with vehicle (6/260) and untreated (1/52) controls. No overall increase in tumors was observed in males of this strain given 17 mg/kg/day of chloroform nor in female ICI/CFLP or male C57BL, CBA or CF/1 strain mice given up to 60 mg/kg/day of chloroform for 1.5 years (Roe et al. 1979).

In a separate experiment, male ICI/CFLP mice were given 60 mg/kg chloroform in arachis oil, as well as in the toothpaste vehicle. There were 12/52 renal tumors in the $CHCl_3$/arachis-oil-treated group compared with 1/52 in arachis oil controls; mice given 60 mg/kg chloroform in the toothpaste vehicle had 5/52 renal tumors (Roe et al. 1979).

In the second study, caesarian-derived SPF Sprague-Dawley rats (50 males, 50 females) were intubated 6 days per week with 60 mg/kg chloroform in a toothpaste vehicle for 80 weeks, followed by 15 weeks of observation. The only noteworthy changes were a depression of plasma (but not erythrocyte) cholinesterase in females, which reversed itself upon cessation of treatment, and a decrease in absolute and relative liver weights of females killed at termination of the study. Females, but not males, possess plasma butyrlcholinesterase activity, which was inhibited by chloroform treatment. No clear histologic evidence of toxic effects on liver or kidney were seen in either sex. A wide spectrum of different types of neoplasms was seen but did not appear to be related to treatment (Palmer et al. 1979).

In the third investigation of this series, Heywood and co-workers (1979) gave beagles 0, 15 or 30 mg/kg chloroform in a toothpaste vehicle (in a gelatin capsule) orally 6 days per week for 7.2 years; the dogs were maintained without treatment for an additional 20-24 weeks. There were 8 dogs of each sex in untreated controls and each treatment level; 16 dogs of each sex were in the vehicle control group. The only significant toxic response was a moderate rise in serum glutamic pyruvic transaminase (SGPT) levels, which peaked during the sixth year of the study. Most of the dogs reverted to normal SGPT values during the post-treatment period. No palpable tumors were noted, but a few subcutaneous nodules thought to be of mammary gland origin were detected. Possible chloroform-related aggregations of vacuolated histiocytes ("fatty cysts") were seen in the livers of several dogs at postmortem; the distribution of nodules of altered hepatocytes and fatty cysts in the liver is presented in Table 17. The distribution of fatty cysts appears to be dose-related. A small number of macroscopically and microscopically visible neoplasms was seen but were predominantly age-related. No neoplasia of liver or kidney was found.

Capel and Williams (1978) investigated the effect of chloroform on the growth of some murine tumors (Lewis lung carcinoma, B16 melanoma, and Ehrlich ascites). Groups of male TO strain mice were given 0, 0.15 or 15 mg/kg of chloroform in their drinking water for varying periods of time either prior to and post-inoculation or only post-inoculation with 1×10^6 tumor cells. Exposure to 0.15 mg/kg chloroform did not enhance the growth or metastasis of Lewis lung carcinoma or significantly increase the number of Ehrlich ascites tumor cells. At the 15-mg/kg chloroform treatment level, however, a significant increase in foci of Lewis lung and Ehrlich tumor cells was noted. Similarly, both chloroform exposure levels resulted in invasion of a greater percentage of organs by B16 melanoma than that seen in controls.

Roe et al. (1968) gave an unspecified number of newborn (C57xDBA 2)F_1 mice either a single subcutaneous 200-ug dose of chloroform before they were 24 hours old or eight daily 200-ug injections during the first week of life. No evidence of carcinogenicity was observed after 77 to 80 weeks.

Thus, ingestion of 90-138 mg/kg of chloroform has been shown to induce both hepatic and renal tumors in experimental animals, although other experiments have yielded contradictory results. The negative results may reflect different vehicles employed to administer chloroform, lack of sensitivity of various test species, populations too small to measure statistically significant and/or the lower dosage levels administered in the Roe et al. (1979) and Palmer et al. (1979) studies compared with the NCI bioassay (1976).

ii. Mutagenesis

No indications of mutagenic activity have been reported in the scientific literature for chloroform. No significant mutations were found at the 8-azaguanine locus in Chinese hamster lung fibroblast cells following 24-hour exposure to 3% chloroform in culture (Sturrock 1977).

Negative results have also been reported for chloroform vapors in microbiol assays conducted with Salmonella typhimurium strains TA100, TA1535 (base-pair mutants) and TA1538 (frameshift mutant), both in the presence and absence of liver microsomal activation (Simmon and Tardiff 1978, Uehleke et al. 1977).

Chloroform also did not induce DNA damage (single-strand breaks) in liver DNA of rats given 200-400 mg/kg of chloroform orally. DNA damage was measured by alkaline elution assay (Petzold and Swenberg 1978).

iii. Teratogenesis

Schwetz et al. (1974) exposed pregnant Sprague-Dawley rats to 30, 100 or 300 mg/kg chloroform in the diet, 7 hours a day on days 6 through 15 of gestation. At 30 mg/kg (diet), an increase in wavy ribs and delayed skull ossification were observed. At 100 mg/kg, a significant incidence of fetal abnormalities such as acuadia, imperforate anus, subcutaneous edema, missing ribs, and delayed ossification of both skull and sternebrae were noted. At the 300 mg/kg exposure level, maternal weight gain and food consumption were markedly reduced. The conception rate in this group was only 15% (3/20) compared with 88% (68/77) in the control group. The non-pregnant bred females in this treatment group exhibited vascular evidence of implantation in the mesometrium, but no intrauterine evidence of implantation. The authors suggest that chloroform may interfere with the process of implantation. Litters from the three dams exposed to 300 mg/kg chloroform had a reduced number of live healing (Torkelson et al. 1976). A single occluded 24-hour application of fetuses and decreased fetal body measurements. The number of fetal resorptions was also increased. These effects do not appear to be related to the anorexia seen in the dams at this exposure level, in that the same degree of starvation (3.7 g food per rat per day on days 6 through 15 of gestation) without exposure to chloroform was neither embryo- nor feto-toxic in a special control group maintained on starvation rations.

In another study, rats administered oral dosages up to 126 mg/kg chloroform on days 6-15 of gestation and rabbits given up to 50 mg/kg orally on days 6-18 of gestation showed no evidence of teratogenicity. Offspring of both species had reduced birth weight at these maternally toxic levels, but not at 50 mg/kg and 35 mg/kg treatment levels for rats and rabbits, respectively, when compared with the short daily oral exposure.

iv. Other Toxicological Effects

Available data indicate species-, strain-, and sex-dependent variations in the acute toxicity of chloroform in laboratory animals (see Table 18). Oral LD_{50} (50% lethal dose) values range from 119 mg/kg to 1400 mg/kg in the mouse to 2000 mg/kg in the rat.

In mice, chloroform toxicity varies according to strain and sex. The oral LD_{50} for chloroform was four times higher in C57BL/6J males than in DBA/2J males with first generation offspring of these two strains (B6D2F1/J), exhibiting a value midway between the parental strains. In addition, the histopathological response to acute exposure to chloroform varied with sex. At doses ≥ 252 mg/kg, males of all three genotypes exhibited necrosis of the proximal convoluted renal tubules and hepatic centrilobular necrosis; only renal tubular necrosis was seen at doses less than 252 mg/kg of chloroform. Females had a similar threshold to hepatic damage without developing renal lesions. Immature or castrated adult males were also resistant to chloroform-induced renal toxicity, but both castrated males and females treated with testosterone became sensitive to chloroform-induced renal toxicity (Hill et al. 1975, Vessell et al. 1976, Hill 1978).

Acute oral exposure to 250 mg/kg chloroform produced fatty infiltration and necrosis of the liver and kidney damage in rats (Torkelson et al. 1976). Jones and co-workers (1958) noted similar findings in mice given 350 mg/kg chloroform orally. The hepatotoxic effects of chloroform have been attributed to the interaction of a reactive metabolite of chloroform with tissue proteins and appears to be related to two factors: (1) the rate of biotransformation and (2) the availability of endogenous hepatic antioxidant, reduced glutathione (GSH). In rodents, hepatic necrosis can be enhanced by pretreatment with hepatic microsomal enxyme inducers and conversely reduced by inhibiting biotransformation (Cresteil et al. 1979, Ilett et al. 1973). Supplying antioxidants such as GSH also reduces the severity of liver necrosis associated with chloroform treatment; the actual mechanism by which GSH reduces tissue damage is not known (Stevens and Anders 1978).

One or two 24-hour applications of chloroform to shaved rabbit abdomen produced hyperemia, necrosis, scab formation, and delayed

TABLE 18. ACUTE TOXICITY OF CHLOROFORM IN LABORATORY ANIMALS

Species	Sex	Route	LD_{50} (mg/kg)	Reference
Mouse ICI Swiss	F	oral	1400 (1120-1680)	Bowman et al. (1978)
ICI Swiss	M	oral	1120 (789-1590)	Bowman et al. (1978)
C5BL/6J	M	oral	489 (386- 594)	Hill et al. (1975)
B6D2F1/J	M	oral	297 (237- 356)	Hill et al. (1975)
DBA/2J	M	oral	119 (103- 148)	Hill et al. (1975)
Swiss Webster	M	intraperitoneal	1,781 (1,484-1,929)	Klassen and Plaa (1966)
---		subcutaneous	704	RTECS (1977)
---		inhalation	134 mg/m^3	Torkelson et al. (1976)
Rat	M	oral	2,000	Torkelson et al. (1976)
300 to 470 g	M	oral	1,182 (1,038-1,336)	Torkelson et al. (1976)
80 to 160 g	M	oral	1,336 (1,182-1,632)	Kimura et al. (1971)
16 to 50 g	M+F	oral	445 (297- 742)	Kimura et al. (1971)
	---	oral	800	RTECS (1977)
Dog	M+F	intraperitoneal	1,483	Brownlee et al. (1953)
	---	inhalation	490 mg/m^3	RTECS (1977)
Rabbit	---	inhalation	289 mg/m^3	RTECS (1977)

1,000 mg/kg to 3,980 mg/kg of chloroform to rabbit abdomen produced extensive necrosis and body weight loss. After 2 weeks, necropsy revealed degeneration of the kidney tubules; the livers were not grossly affected (Torkelson *et al*. 1976).

Instillation into the eyes of rabbits resulted in slight conjunctival irritation and corneal injury, which was not reduced by washing the eye 30 seconds later (Torkelson *et al*. 1976).

Torkelson and co-workers (1976) exposed rats to 123, 245 or 417 mg/m^3 chloroform by inhalation 7 hours per day for 138 and 144 days during a 195- to 203-day period. All males displayed an increased relative kidney weight, cloudy swelling of the renal tubular epithelium, and centrilobular granular degeneration with focal areas of necrosis throughout the liver. Decreased body weight was observed in males at the 50 mg/kg and 85 mg/kg levels, with pneumonia and an increase in the relative liver weight present in the 85 mg/kg male rats. Only an increase in relative kidney weight was noted in females at the lowest treatment level; at the two higher exposure levels, liver and kidney pathology was similar to that seen in male rats. Male rats allowed to recover for 6 weeks after their last exposure to 25 mg/kg chloroform, exhibited no pathological findings. Even at the 85 mg/kg treatment level, terminal blood counts and urine analyses were unaffected and serum levels of urea nitrogen, glutamic-pyruvic transaminase, and alkaline phosphatase were within normal limits, despite liver damage, observed histologically.

Dogs exposed to 123 mg/m^3 chloroform, and rabbits and guinea pigs exposed by inhalation to 123 mg/m^3 or 417 mg/m^3 under the same conditions showed inconsistent liver, kidney, and lung changes (Torkelson *et al*. 1976).

In another study, Miklashevskii (1966) administered 0.4 mg/kg or 35 mg/kg chloroform orally to male guinea pigs for 5 months (daily administration implied, but not stated). No effects were noted at the 0.4-mg/kg dose. At 35 mg/kg, only two of the six guinea pigs survived beyond 3 months. The blood albumin-globulin ratio and blood catalase activity decreased by the end of the first and second months, respectively. Animals that died exhibited fatty infiltration, necrosis, and cirrhosis of liver parenchyma, lipoid degeneration, proliferation of interstitial cells in the myocardium, and acute edema of the submucosal and muscular layers of the stomach.

No mortality was seen in dogs given 30 mg/kg to 120 mg/kg chloroform orally for 12-18 weeks. Vomiting occurred at times in dogs given 30, 60 or 120 mg/kg of chloroform and one of two dogs given 120 mg/kg/day became jaundiced after 4-5 weeks. Marked body weight losses and increased levels of serum glutamic pyruvic transaminase were observed in dogs given 60, 90 or 120 mg/kg/day. At necropsy, liver discoloration and increased liver weight were noted in dogs receiving 45 mg/kg/day and above, but not at the 30-mg/kg treatment level. At 60, 90 and 120 mg/kg, hepatocyte enlargement and vacuolation were seen, together with deposition of fat within the hepatocytes (Heywood *et al*. 1979).

Thus, the acute toxicity of chloroform is species-, strain-, and sex-dependent. Oral LD_{50} values range from 119 mg/kg to 2000 mg/kg, with indications of renal and hepatic necrosis. Dermal contact with chloroform for 24 hours resulted in tissue necrosis in rabbits and instillation into eyes resulted in ocular injury. Subchronic inhalation exposure to chloroform produced liver and kidney pathology in rats, but findings were inconsistent in dogs, rabbits, and guinea pigs.

d. Human Studies

Although there are many documented fatalities from chloroform-induced anesthesia, as well as cases of accidental or intentional ingestion, limited information is available on controlled human exposure to chloroform. Ingestion of 120 ml of chloroform has been survived (Schroeder 1965), while serious illness occurred in another individual after ingestion of only 5 ml (Winslow and Gerstner 1978).

Signs of chloroform poisoning include a characteristic sweetish odor on the breath, dilated pupils, cold and clammy skin, initial excitation alternating with apathy, loss of sensation, abolition of motor functions, prostration, unconsciousness, and eventual death. Central lobular necrosis of the liver and renal damage are the most outstanding pathological findings (Winslow and Gerstner 1978).

Timms and Moser (1975) reported patchy pulmonary infiltrates and acute respiratory distress in a 21-year old man who intentionally injected himself intravenously with a 5-ml bolus of reagent-grade chloroform. Evidence of acute hemolysis was also noted. No hepatic or renal toxicity was seen, probably because of the route of administration and the probable rapid pulmonary clearance of the injected chloroform. The subject returned to normal pulmonary functional status within 3 weeks.

Desalva *et al*. (1975) found no indications of hepatotoxicity in chronic users of a dentifrice and mouthwash containing 3.4% and 0.43% chloroform, respectively, over a one- to five-year period. Estimated daily ingestion was 0.3-0.96 mg/kg per day. Some reversible hepatotoxicity was seen, however, in a ten-year clinical study with patients who ingested a cough suppressant containing 1.6 g to 2.6 g of chloroform daily (∿ 23-37 mg/kg per day) (Wallace 1959).

Dermal exposure to chloroform may cause irritation, erythema, hyperemia, and destruction of the epithelium (Malten *et al*. 1968). Eye contact produces burning, redness of conjunctival tissue, and possible damage to the corneal epithelium. Recovery generally occurs in one to three days (Grant 1974).

The carcinogenic effects of chloroform in rodents, and the detection of chloroform in concentrations up to 300 ug/l in the drinking water of municipalities throughout the United States have raised concern on the human health impact of long-term, low-level exposure to chloroform in public water supplies. Several epidemiologic studies have suggested an association between cancer mortality rates and levels of chloroform in drinking water (Page _et al_. 1976, De Rouen and Diem 1977, Cantor _et al_. 1978, Alavanga _et al_. 1978). Many of these studies, however, are deficient in a number of areas such as: lack of individual exposure data, variations in concentrations in water data, and use of current rather than historical exposure data. Furthermore, cancer rates can be confounded by population mobility patterns; regional trends in diet, tobacco, and alcohol consumption; as well as possible contributions of other sources such as occupation, local extent of industrialization, air pollution, etc. (Kraybill 1978).

In a more direct attempt to assess relative cancer risk associated with exposure to chlorinated drinking water, Alavanga and co-workers (1978) conducted the only case-paired study cited in the scientific literature. These investigators compared individual death certificate data for all females in seven New York State counties for the years 1968 to 1970 that died of gastrointestinal and urinary tract cancer with a corresponding set of matched controls. In three of seven counties studied, the combined gastrointestinal and urinary tract cancers were significantly higher in areas supplied by chlorinated water, but there was no significant difference in the other four counties. Furthermore, the results were complicated by the overriding finding that both cancer and chlorination correlated with urban living and this common relationship would result in the apparent correlation between cancer and chlorination.

Thus, although positive correlations between chloroform in drinking water and increased cancer incidence may be apparent, causal relationships have not been proven on the basis of results from these indirect studies.

2. Bromoform

a. Metabolism

Absorption of bromoform may occur by inhalation, from the gastrointestinal tract, and, to a certain extent, through the skin. Lucas (1928) reported that following administration of bromoform to rabbits either rectally or by inhalation, inorganic bromides could be detected in tissues and urine. Anders and associates (1978) found substantial, dose-dependent elevations in blood carbon monoxide levels in male rats given 1 mmol/kg bromoform intraperitoneally. Enzyme induction by pretreatment with phenobarbital (but not 3-methylcholanthrene) markedly increased the blood carbon monoxide levels seen after bromoform administration compared to saline-treated controls. The administration of SKF 525-A, a known inhibitor of drug metabolism, significantly inhibited _in vivo_ metabolism of bromoform to carbon monoxide.

b. Animal Studies

i. Carcinogenesis

Theiss et al. (1977) reported that bromoform produced a positive response in a pulmonary adenoma bioassay. The administration to strain A male mice of 48 mg/kg bromoform intraperitoneally three times per week for 23 weeks resulted in 1.13± 0.36 lung tumors per mouse $p = 0.041$) compared with 0.27 ± 0.15 tumors for vehicle controls. A higher bromoform dosage (100 mg/kg), however, failed to produce a significant pulmonary response (0.67 ± 0.21 lung tumors; $p = 0.136$) under the same treatment conditions.

Bromoform is currently being tested for carcinogenicity by the standard bioassay protocol of the National Cancer Institute.

ii. Mutagenesis

Bromoform vapor tests positive in the Ames system (Simmon and Tardiff 1978). Exposure to the vapor phase of 50 ul of bromoform was mutagenic in *Salmonella typhimurium* TA 100 with or without metabolic activation. A weak response was also reported for strain TA 1535 exposed to the vapor phase of 100-ul of bromoform.

iii. Teratogenesis

No data are available regarding teratogenic effects due to bromoform.

iv. Other Toxicologic Effects

Little is known of the toxicity of bromoform. Bowman et al. (1978) recently reported oral LD_{50} values of 1400 mg/kg (1205-1595) and 1550 mg/kg (1165-2065) in male and female ICR Swiss mice. Males appeared to be more sensitive than females to the acute lethal effects of bromoform. Ataxia, sedation, and anesthesia occurred within 60 minutes of oral administration of 1000 mg/kg of bromoform, but not at lower dosages. Sedation persisted for approximately 4 hours. Subcutaneous LD_{50} values of 410 mg/kg and 1820 mg/kg bromoform have also been reported for the rabbit and mouse, respectively (RTECS 1977, Kutob and Plaa 1962).

In dogs, deep narcosis occurred after 8-minute exposure to 142,100 mg/m^3 bromoform; mortality occurred after 60 minutes. Exposure to the same concentration for 30 minutes produced deep narcosis, but the dogs survived (Sax 1979).

Inhalation by rats of 0.25 mg bromoform per liter of air for 4 hours per day for 2 months produced disorders in prothrombin synthesis and glycogenesis in the liver and reduced renal filtration capacity; the threshold concentration was 0.05 mg/liter (Dykan 1962).

c. Human Studies

Little information is available on the adverse health effects of bromoform in man. Sax (1979) reports that inhalation of small amounts of bromoform causes irritation provoking lacrimation, salivation and facial hyperemia. Poisonings with bromoform have been reported (Patty 1963). Symptoms include listlessness, headache, vertigo, unconsciousness, loss of reflexes, and occasionally convulsions. The primary cause of death is respiratory failure.

3. Dibromochloromethane

a. Metabolism

Anders et al. (1978) found a slight elevation of blood carbon monoxide levels in male rats given 1 mmol/kg of dibromochloromethane by intraperitoneal injection. At 2 hours, blood levels of carbon monoxide were approximately 400 mmol CO/ml compared with a value of 50 mmol CO/ml for controls.

b. Animal Studies

i. Carcinogenesis

No data are currently available concerning the carcinogenicity of dibromochloromethane. The compound is currently being tested (June 1979) for carcinogenicity by the National Cancer Institute according to its standard bioassay protocol.

ii. Mutagenesis

Simmon and Tardiff (1978) reported a positive mutagenic effect in *Salmonella typhimurium* TA 100 (with or without metabolic activation) exposed to vapor from 10 ul of dibromochloromethane in a dessicator.

iii. Teratogenesis

No data are available concerning the teratogenesis of dibromochloromethane.

iv. Other Toxicologic Effects

Toxicological data on dibromochloromethane are sparse. Bowman et al. (1978) recently reported oral LD_{50} values of 800 mg/kg (667-960) and 1200 mg/kg (945-1524) dibromochloromethane for male and female ICR Swiss mice, respectively. Males appeared to be more sensitive than females to the acute lethal effects of dibromochloromethane. Sedation and anesthesia occurred within 30 minutes following oral administration of 500 mg/kg of this compound and persisted for approximately 4 hours. At necropsy, livers appeared to have fatty infiltration, the kidneys were pale, and hemorrhaging was noted in the brain, lungs, and adrenals.

c. Human Studies

No human data are available.

4. Dichlorobromomethane

a. Metabolism

Male rats injected intraperitoneally with 1 mmol/kg dichlorobromomethane revealed only a small elevation in blood levels of carbon monoxide. At 2 hours following injection, blood carbon monoxide levels were approximately 50 mmol and 120 mmol CO/ml for control and dichlorobromomethane-treated rats, respectively (Anders *et al*. 1978).

b. Animal Studies

i. Carcinogenesis

Theiss *et al*. (1977) reported that dichlorobromomethane produced an elevated response in a pulmonary adenoma bioassay that approached statistical significance. Strain A male mice were injected intraperitoneally three times per week for 24 weeks with 0, 20, 40 or 100 mg/kg dichlorobromomethane. The incidence of lung tumors per mouse (± SE) were 0.27 ± 0.15, 0.20 ± 0.11 ($p = 0.724$), 0.25 ± 0.11 ($p = 0.930$) and 0.85 ± 0.27 ($p = 0.067$), respectively.

Dichlorobromomethane is currently being tested (June 1979) by the National Cancer Institute according to its standard bioassay protocol.

ii. Mutagenesis

Dichlorobromomethane (50 ul) was mutagenic in *Salmonella typhimurium* strain TA 100, both in the presence and absence of metabolic activation (Simmon and Tardiff 1978).

iii. Teratogenesis

No data are available concerning teratogenic effects of dichlorobromomethane.

iv. Other Toxicologic Effects

As is the case for dibromochloromethane, the toxicologic data available for dichlorobromomethane are quite limited. Male ICR Swiss mice appear to be more sensitive than females to the acute lethal effects of dichlorobromomethane. Oral LD_{50} values of 450 mg/kg (326-621) and 900 mg/kg (811-999) of dichlorobromomethane were recorded for males and females of this strain, respectively. Sedation and anesthesia occurred within 30 minutes after oral administration of 500 mg/kg of this compound and persisted for approximately 4 hours. At necropsy, livers appeared to have fatty infiltration, kidneys were pale, and hemorrhaging was observed in the adrenals, lungs, and brain (Bowman *et al*. 1978).

c. Human Studies

No data are available.

5. Overview

Trihalomethanes are present in the chlorinated drinking water supply of municipalities throughout the United States. Several epidemiological studies have suggested a correlation between ingestion of chlorinated water and a higher incidence of cancer. The four trihalomethanes of concern are chloroform, bromoform, dibromochloromethane, and dichlorobromomethane.

Extensive toxicologic data on chloroform indicate that it is rapidly absorbed through the lungs, from the gastrointestinal tract and, to a lesser extent, through intact skin. Species variations exist with regard to the metabolic handling of chloroform, but some conversion to carbon dioxide does occur.

Ingestion of 90-138 mg/kg of chloroform has been shown to induce both hepatic and renal tumors in experimental animals, although other experiments at lower dosage levels have yielded contradictory results. No indications of mutagenic activity have been reported.

Administration by inhalation to rats during days 6-15 of gestation resulted in a high incidence of fetal resorption and a few cases of acudate fetuses. No evidence of teratogenicity was found in another study, in which pregnant rats and rabbits were given up to 126 and 50 mg/kg, respectively, by oral intubation.

Species-, strain-, and sex-related differences exist with respect to the acute lethal effects of chloroform, and both acute and prolonged exposure to chloroform results in liver necrosis and kidney damage.

In man, ingestion of 120 ml of chloroform has been survived, but serious illness has been reported following ingestion of only 5 ml. Dermal contact produces burning pain within a few minutes of exposure and, depending on dose, erythema, hyperemia, and vesication may also occur.

Limited toxicologic information is available for bromoform, dibromochloromethane, and dichlorobromomethane. However, because of structural similarities to chloroform, all three compounds are cause for concern with regard to carcinogenic effects. Preliminary results in lung adenoma bioassays with bromoform and dichlorobromomethane support this concern. In addition, all three of the lesser trihalomethanes are mutagenic in the Ames test. To date, other adverse health effects have not been demonstrated, and therefore cannot be quantitated.

B. HUMAN EXPOSURE

1. Introduction

This section quantifies the exposure of persons in the U.S. to trihalomethanes. Several authors have attempted such an analysis previously (NAS 1978, U.S. EPA 1979a). However this discussion will include some new data, as well as briefly review previous estimations of exposure. The exposure routes considered include ingestion via drinking water and food, inhalation, and dermal contact.

2. Ingestion

a. Drinking Water

The formation of trihalomethanes during chlorination of water supplies has been discussed in Chapters III and IV. The concentrations of these chemicals in drinking water have been measured in several nationwide surveys. The National Organics Reconnaissance Survey (NORS) (Symons et al. 1975) included sampling of trihalomethanes in raw and finished water from 80 water supplies. The National Organic Monitoring Survey (NOMS)(U.S. EPA 1978) also included analysis for these chemicals, in addition to others, in samples taken from 113 community water supplies during a 12-month period. The results from these surveys have been analyzed and presented in numerous ways, and have been used in various risk assessments (NAS 1978, U.S. EPA 1979a, Reitz et al. 1978). As a result, these data are not discussed extensively here. The reader is referred to the original sources and the discussions cited above.

Table 19 shows the concentrations of trihalomethanes found in the NORS and NOMS surveys (Symons et al. 1975, U.S. EPA 1978). Figure 6 shows the distribution of total trihalomethanes in drinking water from NOMS. Concentrations of total trihalomethanes are greater than 200 ug/l (see Table 20) and chloroform levels exceed 100 ug/l in many of the locations sampled.

The formation of trihalomethanes in chlorinated water supplies has been discussed in Chapter IV. It is obvious that water source, treatment method, and analytical method influence the observed levels of trihalomethanes. The samples collected for NORS were of finished water at the plant, while the terminal samples reported in NOMS had been allowed to react with residual chlorine. Sylvia et al. (1978) showed that samples collected in the distribution system had much higher levels than those collected at the plant. U.S. EPA (1978) showed that the terminal samples contained higher levels than those that had been quenched (sodium thiosulfate added to react with residual chlorine). However, measurements taken in the distribution system generally showed levels between those of the quenched and terminal samples. Therefore, use of these values either underestimates or overestimates actual exposure levels.

TABLE 19. CONCENTRATIONS OF CHLOROFORM, BROMOFORM, BROMODICHLOROMETHANE, AND DIBROMOCHLOROMETHANE AND TOTAL TRIHALOMETHANES IN WATER SUPPLIES FROM NORS AND NOMS

	Concentration (mg/1)				
	NORS	NOMS			
		Phase I	Phase II (summer)	Phase III (winter)	
Trihalomethanes				Quenched	Terminal
Chloroform					
Median	0.021	0.027	0.059	0.022	0.044
Mean	-	0.043	0.083	0.035	0.069
Range	NF[1]-0.311	NF-0.271	NF-0.47	NF-0.20	NF-0.540
Bromoform					
Median	0.005	LD[2]	LD	LD	LD
Mean	-	0.003	0.004	0.002	0.004
Range	NF-0.092	NF-0.039	NF-0.280	NF-0.137	NF-0.190
Dibromochloromethane					
Median	0.001	LD	0.004	0.002	0.003
Mean	-	0.008	0.012	0.006	0.011
Range	NF-0.100	NF-0.19	NF-0.290	NF-0.114	NF-0.250
Bromodichloromethane					
Median	0.006	0.010	0.014	0.006	0.011
Mean	-	0.018	0.018	0.009	0.017
Range	NF-0.116	NF-0.183	NF-0.180	NF-0.072	NF-0.125
Total Trihalomethanes					
Median	0.027	0.045	0.087	0.037	0.074
Mean	0.067	0.068	0.117	0.053	0.100
Range	NF-0.482	NF-0.457	NF-0.784	NF-0.295	NF-0.695

Source: U.S. EPA (1978)

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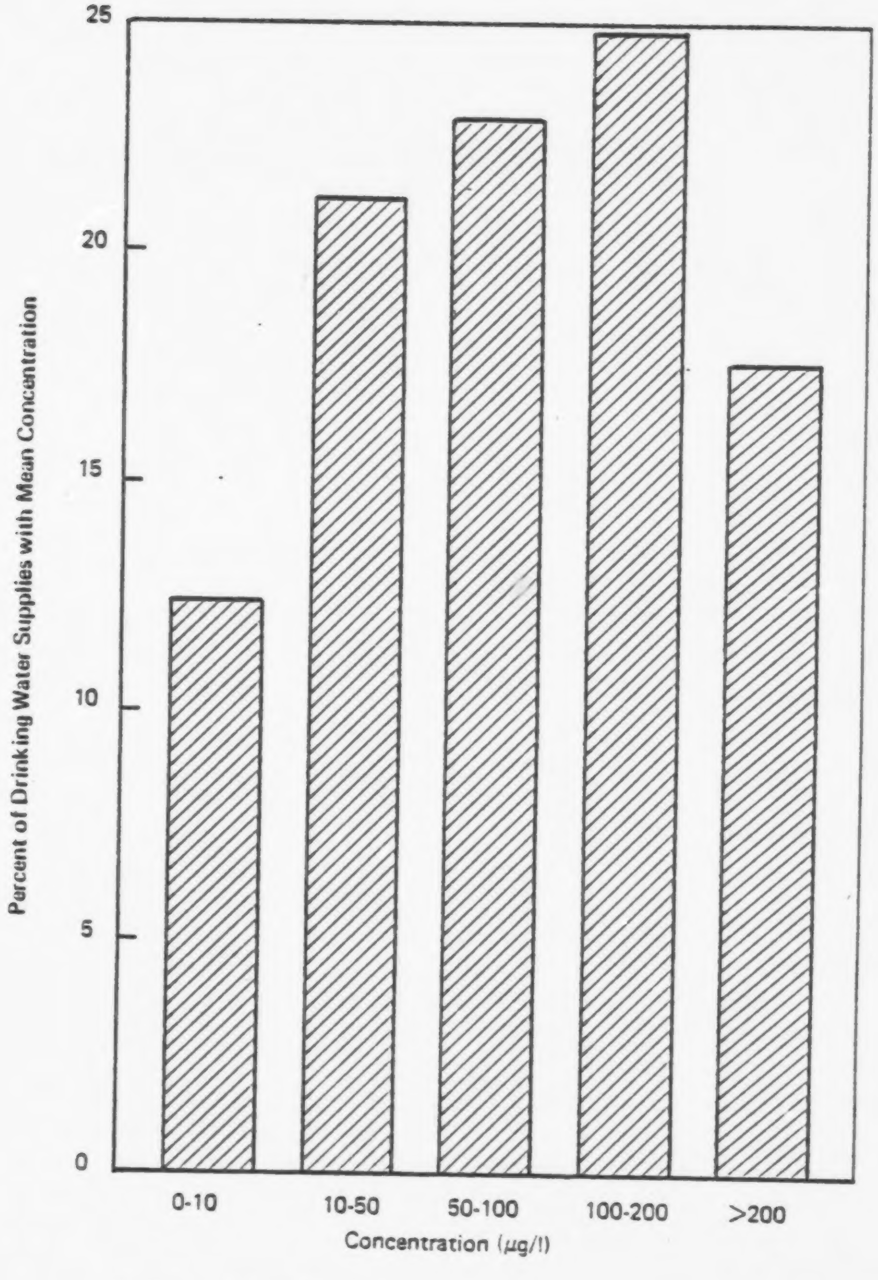
[1] NF = not found.

[2] LD = less than detection limit.



Source: U.S. EPA (1978)

FIGURE 6 DISTRIBUTION OF CONCENTRATIONS OF TOTAL TRIHALOMETHANES IN MAJOR U.S. DRINKING WATER SUPPLIES

TABLE 20. SAMPLING LOCATIONS FOR NOMS WITH CONCENTRATIONS OF TOTAL TRIHALOMETHANES GREATER THAN 200 ug/1

Location	Concentration[1]
Annondale, VA	230
Brownsville, TX	670
Camden, AR	250
Cape Cirardeau, MO	290
Charleston, SC	230
Columbus, OH	250
Hagerstown, MD	200
Houston, TX	460
Huntington, WV	230
Huron, SD	260
Illwaco, WA	260
Jackson, MS	270
Louisville, KY	240
Melbourne, FL	780
Montgomery, AL	210
Newport, RI	310
Norfolk, VA	250
Oklahoma City, OK	200
Omaha, NE	210
Tampa, FL	340
Terre Bonne Parish, LA	230
Wheeling, WV	310

[1] Phase II; summer terminal.

Source: U.S. EPA (1978)

Table 21 shows the exposures of persons to chloroform estimated with various assumptions regarding daily intake of water and the concentration of chloroform. The range of exposures was estimated to be 0.02-1.2 mg chloroform per day. These estimates are based on the assumption that all water used in water-based beverages comes from the same source of tap water. Though this assumption may be valid for beverages such as coffee and tea, chloroform levels in soft drinks, beer, wine, etc. would correspond to the levels in drinking water in the area of manufacture and not necessarily to the levels in the area of consumption.

Table 22 shows median and maximum exposures for all of the four trihalomethanes. Though some high concentrations of bromoform, dibromochloromethane, and bromodichloromethane are found in drinking water, exposure levels for these other trihalomethanes are generally much lower than exposure levels for chloroform.

b. Food

Little information is available on the levels of chloroform in food. McConnell et al. (1975) apparently have done the only work to date. They analyzed various foods in Great Britain and found chloroform levels ranging from 0 ug/kg to 33 ug/kg. The higher levels were found in cheeses, olive oil, tea packets, and potatoes. The source of this contaminant is unknown, although chloroform has been used as a pesticide. It is possible that chloroform may be formed in the food from other organics. NAS (1978) used these data to estimate human exposure to chloroform through food. For the minimum intake of food containing the minimum concentration of chloroform, exposure is estimated to be 0.0006 mg/day; for the maximum intake and maximum concentration, the exposure would be 0.04 mg/day. The average is estimated to be 0.006 mg/day. These estimates are based on concentrations of chloroform in uncooked food; since cooking is likely to vaporize some of the chloroform, the estimated exposure levels are probably overstated. No information is available on the levels of the other trihalomethanes in food.

3. Air

Section IV-C described levels of chloroform in both urban and rural air. In order to simplify these data for use in exposure estimates, the following assumptions were made:

Exposure Setting	Concentration of Chloroform (ug/m^3)
rural atmosphere	0.07
urban atmosphere	1
industrial atmosphere	50
indoor atmosphere	0.5

TABLE 21. ESTIMATED HUMAN EXPOSURES TO CHLOROFORM VIA DRINKING WATER IN THE U.S.

	Estimated Exposure to Chloroform (mg/day)^{1,2}			
Exposure Category	Minimum Intake	Maximum Intake	Reference Male	Reference Female
Adult				
median concentration (0.059 mg/1)	0.02	0.13	0.10	0.07
maximum concentration (0.540 mg/1)	0.20	1.18	0.90	0.65
Child				
median concentration (0.059 mg/1)	0.03	0.05	0.06	-
maximum concentration (0.540 mg/1)	0.29	0.43	0.51	-

[1] Includes tap water and water-based beverages.

[2] Intakes - Adult - 365-2180 ml/day. Taken from ICRP (1975)
Children - 540-790 ml/day
reference male - 1650 ml/day
reference female - 1200 ml/day
reference child - 950 ml/day (It is unclear why this is not within the range shown above.)

Source: Arthur D. Little, Inc.

TABLE 22. ESTIMATED HUMAN EXPOSURES TO TRIHALOMETHANES VIA DRINKING WATER

Trihalomethane	Concentration (mg/l)		Daily exposure (mg/day)	
	Median	Maximum	Assuming Maximum Adult Intake[1] and Maximum Concentration in Water	Assuming Reference Male Intake[2] and Median Concentration in Water
Chloroform	0.059	0.540	1.2	0.1
Bromoform	0.004	0.280	0.6	0.007
Dibromochloromethane	0.004	0.290	0.6	0.007
Bromodichloromethane	0.014	0.180	0.4	0.02

[1] 2.18 liter per day

[2] 1.65 liter per day

Source: Arthur D. Little, Inc.

These levels were selected to represent typical conditions, although there is considerable controversy over what may be considered typical since the range in values is so great. The value for the indoor occupational atmosphere is intended to represent concentrations commonly found in such locations as beauty parlors, drug stores, photoduplicating rooms, etc. Presumably persons working in these situations would be exposed for 8-hour periods. Persons using these services would be exposed for shorter periods, perhaps up to 4 hours per exposure, as in the case of beauty parlors.

Table 23 gives the estimated exposures associated with the above concentrations. These estimates were developed for a respiratory volume for light activity of 19200 l for 16 hours and 3600 l for 8 hours of resting (ICRP 1975). Higher respiratory volumes, such as those for athletes or other more active people, would result in correspondingly higher exposure levels.

Monitoring data are insufficient to permit an estimate of the size of the population exposed at these levels. The urban exposure level shown in Table 23 may be quite common, and exposures at this level for 24 hours would not be unusual. The estimate of 0.5 mg/day would be expected for persons who work in the highly industrialized cities in the U.S. Unfortunately, no estimates of exposure can be made for the other trihalomethanes, but the exposure levels would be expected to be considerably lower.

4. Dermal Contact

Absorption of trihalomethanes through the skin would be expected to occur in areas where the water supply is chlorinated. Blank (personal communication, as cited in Beech 1980) has measured the permeability constant of 125 x 10^{-3} cm/hr for chloroform. For the median concentration of 60 ug/l in water, an exposure of 0.15 mg/hr is estimated for a total body exposure. If total body immersion occurs for 2 hours/day, the total maximum exposure would be 0.3 mg/day. A more typical immersion would be 0.2 hours/day including bathing and dishwashing (U.S. EPA 1979c), resulting in an average exposure of 0.03 mg/day. Similar calculations can be made for the other trihalomethanes. Using the same permeability constant and median concentrations in water, exposures of 0.002-0.006 mg/day were estimated for this route. Maximum exposures ranged from 0.08-0.14 mg/day.

Beech *et al*. (1980) have measured the concentration of trihalomethanes in swimming pools in Florida and found mean concentrations of 156 ug/l in freshwater pools (mainly chloroform) and 657 ug/l in saline pools (mainly bromoform). The maximum concentrations were 430 ug/l and 1278 ug/l, respectively. These authors suggested that trihalomethanes are continuously formed in swimming pool water. Using the permeability constant as above for chloroform and bromoform, several estimates of exposure were made for a six-year old child, as shown in Table 24.

TABLE 23. ESTIMATED CHLOROFORM EXPOSURES VIA INHALATION

Exposure Situation	Chloroform Concentration (ug/m3)	Chloroform Exposure (mg/day)
Rural	0.07	0.002
Urban (24 hours)	1	0.02
Urban (8 hours) indoor (16 hours)	1, 0.5	0.02
Industrial (8 hours) indoor (16 hours)	50,0.5	0.5

Source: Arthur D. Little, Inc.

TABLE 24. EXPOSURE OF A CHILD TO TRIHALOMETHANES IN SWIMMING POOLS

Type of Pool	Exposure (mg/day) Typical[1]	Exposure (mg/day) Maximum[2]
freshwater (chloroform)	0.2	1.3
saltwater (bromoform)	0.7	4.2

[1] Assumes a total exposure (0.88×10^4 cm^2) of 1 hour per day at the mean concentrations of 156 ug/l and 657 ug/l for chloroform and bromoform, respectively.

[2] Assumes an exposure of 3 hours per day at the maximum concentrations of 430 ug/l and 1278 ug/l, respectively.

Note: The permeability constant of 125×10^{-3} cm/hour was used for all calculations.

Source: ADL estimates, from Beech (1980)

5. Conclusions

Both inhalation and ingestion of chloroform in drinking water appear to be important exposure routes. The relative importance of these two exposure routes depends upon the location. Inhalation may be more important in highly industrialized areas, whereas chloroform in drinking water may be more important where water is chlorinated and levels in air are low. Ingestion of chloroform in food does not appear to be an important exposure route. Dermal contact of persons spending long periods in swimming pools may result in high exposures to chloroform.

Exposure to the other trihalomethanes occurs primarily through drinking water, although dermal contact with these compounds may result in significant exposure in some situations. The results in Table 24 suggest that dermal exposures can be high for persons spending a significant amount of time in swimming pools. It should be noted that inhalation exposures would probably be occurring at the same time. Beech (1980) calculated that inhalation exposures would be about one-half as large as dermal exposures under the same conditions.

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CHAPTER VI

EFFECTS AND EXPOSURE -- AQUATIC BIOTA

A. EFFECTS OF TRIHALOMETHANES ON AQUATIC ORGANISMS

1. Introduction

This section provides information about the levels of trihalomethanes that disrupt the normal behavior and metabolic processes of aquatic organisms. Despite a thorough literature search, no toxicity data for dibromochloromethane or dichlorobromomethane were found. Moreover, information on chloroform and bromoform was limited. In assessing threshold effects levels, it is important to note that, with few exceptions, the bioassays were conducted under static conditions, and the toxicant concentrations were calculated rather than measured. Consequently, the LC_{50} values (concentrations lethal to 50% of test organisms) reported could underestimate actual toxicity, as a result of toxicant evaporation and metabolism by test organisms.

2. Chloroform

Earlier studies on the aquatic toxicity of chloroform reported "negative" (avoidance) reactions as a measure of effects levels. Clayberg (1917) observed "positive reactions" (not defined) in brown bullheads and white suckers in 214 mg/l of chloroform, and "a few negative reactions . . . in somewhat higher concentrations." Jones (1974) recorded an avoidance reaction by the ten-spined stickleback in 100 mg/l. Fifty percent of a group of goldfish were anesthetized by a 167 mg/l solution of chloroform (Cherkin and Catchpool 1964). This effect was observed to decrease with increasing temperature.

More recent research on the acute toxicity of chloroform has yielded lower overall effects levels than the studies described above. The lowest reported 96-hour LC_{50} value for a marine organism is 28 mg/l, for the dab (Pearson and McConnell 1975). Equally susceptible is Daphnia magna, with a 48-hour LC_{50} value of 28.9 mg/l chloroform (U.S. EPA 1978a). The "chronic value" (as defined by U.S. EPA) for this species is 2.5 mg/l. The 96-hour LC_{50} for the pink shrimp, a marine invertebrate, is 81.5 mg/l, as reported by Bentley *et al*. (1975).

Clayberg (1917) observed mortality in the orange-spotted sunfish after 1 hour of exposure to concentrations ranging from 107 mg/l to 153 mg/l.

Anderson *et al*. (1979) conducted 96-hour acute toxicity bioassays with largemouth bass, rainbow trout, and bluegill sunfish. The respective LC_{50} values for chloroform were 45-56 mg/l, 15-22 mg/l, and 13-22 mg/l. In a comparative study, Bentley *et al*. (1975) found rainbow trout to be more sensitive to chloroform than bluegill sunfish, with respective 96-hour LC_{50}'s of 66.8 mg/l and 115.0 mg/l in water 35 mg/l hardness. When the hardness was increased to 200 mg/l and the bioassays repeated, 96-hour LC_{50}'s values decreased to 43.8 mg/l and 110.0 mg/l, respectively, a reduction indicating significantly greater toxicity in hard water for the rainbow trout. The data available regarding the toxicity of chloroform to aquatic organisms are summarized in Table 25.

3. Bromoform

The data for bromoform are limited and are all based on static bioassays. The bluegill sunfish was the only freshwater finfish tested for sensitivity to bromoform. The 96-hour LC_{50} for this species was 29.3 mg/l. *Daphnia magna* experienced median lethality after 48 hours of exposure to 46.5 mg/l bromoform. For the alga (*Selenastrum capricornutum*), the 96-hour EC_{50} (effects observed in 50% of test organisms) level was 172 mg/l with respect to chlorophyll-*a* activity, and 116 mg/l as determined by cell number (U.S. EPA 1978b).

The effects of bromoform were also measured for three marine species. The 96-hour LC_{50} for the sheepshead minnow was 17.9 mg/l bromoform, while the chronic value was 9.2 mg/l. The mysid shrimp was apparently somewhat less susceptible to bromoform, with a 96-hour LC_{50} value of 24.4 mg/l. The alga, *Skeletonema costatum*, was tested for bromoform effects in terms of chlorophyll-*a* activity and proportion of cells affected. The respective 96-hour EC_{50} concentrations were 12.3 mg/l and 11.5 mg/l, respectively (U.S. EPA 1978b).

In a study by Gibson *et al*. (1979), five marine species were tested for sensitivity to bromoform in continuous-flow bioassays. An LC_{50} value was not obtained for the littleneck clam (*Protothaca staminea*) because, in high concentrations of bromoform, the clams closed up and did not pump water. However, mortality was observed in 5 mg/l and 10 mg/l bromoform. At concentrations above 10 mg/l, the Atlantic oyster (*Crassostrea virginica*) and the quahog (*Mercenaria mercenaria*) also closed and did not circulate water, and this resulted in no mortalities during the 96-hour bioassay. However, when exposure was continued for an additional 3 days, several organisms died. Ninety-six-hour LC_{50} concentrations were then estimated at 40 mg/l for the oyster, and 140 mg/l for the quahog. For the brown shrimp (*Penaeus aztecus*) and the menhaden (*Brevoortia tyrannus*), 96-hour LC_{50} values were given as 26 mg/l and 12 mg/l, respectively. These data are summarized in Table 26.

4. Summary

The LC_{50} values for the bluegill included the lowest and highest values recorded, from 13 mg/l to 115 mg/l chloroform. *Daphnia magna* and rainbow trout were found to be comparatively sensitive, with LC_{50} values for chloroform of 28.9 mg/l and 15 mg/l, respectively. The limited data do not indicate whether marine or freshwater species are generally more sensitive to chloroform. In one bioassay, rainbow trout were significantly more susceptible in hard water than in soft water. No data were available on the toxicity of chloroform to aquatic plants.

TABLE 25. EFFECTS OF CHLOROFORM ON AQUATIC ORGANISMS

Concentration (mg/l)	Species	Hardness (mg/l) Salinity o/oo	pH	Temperature	Test Type	Test Duration	Effects	Reference
28	Dab (*Limanda* sp.)	~30 o/oo	-	-	Flow-through	96 hr	LC_{50}	Pearson and McConnell (1975)
28.9	*Daphnia magna*	-	-	-	Static unmeasured	48 hr	LC_{50}	U.S. EPA (1979a)
43.8	Rainbow trout (*Salmo gairdneri*	200 mg/l	7.1	12°C	Static nominal	96 hr	LC_{50}	Bentley *et al.* (1975)
66.8	Rainbow trout (*Salmo gairdneri*)	35 mg/l	7.1	12°C	Static nominal	96 hr	LC_{50}	Bentley *et al.* (1975)
81.5	Pink shrimp (*Penaeus duorarum*)	25 o/oo	8.0	20°C	Static nominal	96 hr	LC_{50}	Bentley *et al.* (1975)
100	Ten-spined stickleback (*Pygosteus pungitius*)	-	-	15°C	Flow-through	~1 hr	Negative reaction	Jones (1974)
106.89-152.7	Orange-spotted sunfish (*Lepomis humilis*)	-	-	-	-	1 hr	Death	Clayberg (1917)
110.0	Bluegill sunfish (*Lepomis macrochirus*)	35 mg/l	7.1	21°C	Static nominal	96 hr	LC_{50}	Bentley *et al.* (1975)
115.0	Bluegill sunfish (*Lepomis macrochirus*)	200 mg/l	7.1	21°C	Static nominal	96 hr	LC_{50}	Bentley *et al.* (1975)
167	Goldfish (*Carassius auratus*)	-	-	20°C	Static	30-60 min	50% anesthesia	Cherkin and Catchpool (1964)
>213.8	Brown bullhead (*Ictalurus nebulosus*)	-	-		-	1 hr	Negative reaction	Clayberg (1917)
>213.8	White sucker (*Catostomus commersoni*)	-	-	-	-	-	Negative reaction	Clayberg (1917)

TABLE 26. EFFECTS OF BROMOFORM ON AQUATIC ORGANISMS

Concentration (mg/l)		Water	Test Duration	Effects	References
5	Littleneck clam (*Protothaca staminea*)	Marine	96 hr	Mortality	Gibson *et al*. (1979)
9.2	Sheepshead minnow (*Cyprinodon variegatus*)		-	Chronic Value	U.S. EPA (1978)
	Alga (*Skeletonema costatum*)				
11.5	cell number		96 hr	EC_{50}	U.S. EPA (1978)
12.3	chlorophyll-*a*		96 hr	EC_{50}	U.S. EPA (1978)
12	Menhaden (*Brevoortia tyrannus*)	Marine	96 hr	LC_{50}	Gibson *et al*. (1979)
17.9	Sheepshead minnow (*Cyprinodon variegatus*)	Marine	96 hr	LC_{50}	U.S. EPA (1978)
24.4	Mysid shrimp (Mysidopsis bahia)	Marine	96 hr	LC_{50}	U.S. EPA (1978)
26	Brown shrimp (Penaeus aztecus)	Marine	96 hr	LC_{50}	Gibson *et al*. (1979)
29.3	Bluegill sunfish (*Lepomis macrochirus*)	Freshwater	96 hr	LC_{50}	U.S. EPA (1978)
40	Atlantic oyster (*Crassostrea virginica*)	Marine	96 hr	LC_{50}	Gibson *et al*. (1979)
46.5	*Daphnia magna*	Freshwater	48 hr	LC_{50}	U.S. EPA (1978)
	Alga (*Selenastrum capricornutum*)				
112	chlorophyll-*a*		96 hr	EC_{50}	U.S EPA (1978)
116	cell number		96 hr	EC_{50}	U.S. EPA (1978)

Although information on bromoform toxicity was equally scarce, bromoform appears to be somewhat more toxic to aquatic life than chloroform. The LC_{50} values ranged between 12 mg/l for the menhaden and 46.5 mg/l for *Daphnia magna* (the one species tested that exhibited less sensitivity to bromoform than to chloroform). For the marine alga species tested, EC_{50} concentrations were 11.5 mg/l and 12.3 mg/l, approximately one order of magnitude less than for the freshwater alga.

B. EXPOSURE OF AQUATIC BIOTA TO TRIHALOMETHANES

Monitoring data for the trihalomethanes considered here are extremely sparse; consequently, any generalizations made with regard to exposure levels must be strictly qualified. Since the levels observed were in many cases at or below the detection limits of the analytic procedure, future improvements in detection ability could conceivably lower the estimates made below.

Ambient concentrations of chloroform in water normally fell between 0.1 ug/l and 10 ug/l, with a small proportion of measurements exceeding 10 ug/l (see Chapter IV). In a few instances the levels exceeded 100 ug/l. Nearly all (97%) of the bromoform measurements were between 1.0 ug/l and 10 ug/l. Roughly two-thirds of observations concerning both bromodichloromethane and dibromochloromethane fell into the 0.1-1.0 ug/l category, with approximately one-third exceeding 1.0 ug/l. The Pacific Northwest and California basins were the most intensively sampled watersheds for the latter two trihalomethanes. Perhaps coincidentally, the concentrations in the Pacific Northwest for both were usually between 1.0 ug/l and 10 ug/l, while California had similar levels of dibromochloromethane.

In addition, no fish kills attributed to chloroform have been reported in the data files of the Monitoring and Data Support Division, Office of Water Regulations and Standards, U.S. EPA.

Most of the data for bromoform, bromodichloromethane, and dibromochloromethane were remarked, which probably means the chemical was detected but the concentration was not quantified. However, the fact that the levels of all of the trihalomethanes were usually so low as to approach the detection limits may suggest that ambient exposure levels in most areas of the U.S. are negligible. Factors that modify the toxicity of trihalomethanes for aquatic biota have not been identified or studied sufficiently to merit a discussion of geographical variations in such factors.

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CHAPTER VII. RISK CONSIDERATIONS

A. INTRODUCTION

This chapter assesses risk to both humans and non-humans associated with exposure to chloroform, bromoform, dibromochloromethane, and bromodichloromethane. However, only the risks associated with exposure to chloroform can actually be quantified, since sufficient information on exposure and effects was not available for the other three trihalomethanes.

Several different dose-response models were applied to the available data concerning the carcinogenic effects of chloroform, and the range of potential human risk was estimated for various possible exposure levels. These risk estimates have been compared against other risk estimates derived from the literature, although the latter usually focus upon drinking water alone as the pathway of exposure.

With respect to non-human biota, little information is available on the effects of environmental exposure to trihalomethanes; therefore risks to non-human biota were addressed only in qualitative terms.

B. RISK TO HUMANS

1. Effects of Trihalomethanes

Chapter V discusses the effects of trihalomethanes in laboratory animals and humans in some detail. Tables 27-30 summarize these effects. Chloroform has been shown to be carcinogenic in rats and mice. However, no evidence indicates teratogenicity or mutatagenicity. Acute effects attributable to chloroform include liver necrosis and kidney damage. It is likely that these effects would not be observed in the general population at the present exposure levels.

The other three trihalomethanes have not been tested for carcinogenicity; however, they all are potential mutagens based on the results of the Ames bioassay.

As a result of the available data, the only risks that can be quantified at this time are the potential cancer risks due to chloroform exposure, which are considered below.

2. Carcinogenicity of Chloroform

The potential carcinogenic effects of chloroform upon humans can be quantitatively estimated through extrapolation of *in vivo* laboratory results. The available data concerning mammalian effects were discussed previously in Chapter V and summarized in Table 27. For extrapolation purposes, the NCI data shown in Table 31 have been selected.

TABLE 27. ADVERSE EFFECTS OF CHLOROFORM ON MAMMALS

Adverse Effect	Species	Lowest Reported Effect Level	No Apparent Effect Level
Hepatocellular Carcinoma	Mouse	138 mg/kg (diet)	----
Renal Epithelial Tumors	Rat	90 mg/kg (diet)	----
Teratogenesis	Mouse	60 mg/kg (gavage)	17 mg/kg
	Rat	490 $mg/m^3/hr$ inhal	----
	Rat	----	126 mg/kg (orally)
	Rabbit	----	50 mg/kg (orally)
Hepatic and Renal Necrosis	Rat Mouse	250 mg/kg (orally)	----
Oral LD_{50}	Mouse	119 mg/kg	----

Source: Chapter V.

TABLE 28. ADVERSE EFFECTS OF BROMOFORM ON MAMMALS

Adverse Effect	Species	Lowest Reported Effect Level	No Apparent Effect Level
Pulmonary Adenoma	Mouse	48 mg/kg ip x 23	4 mg/kg ip x 18
Mutagenicity	*Salmonella typhimurium* TA 100	50 ul (vapor)	---
Teratogenicity	---	No data available	---
Chronic Toxic Effects	---	No data available	---
Median Oral Lethal Dose	Mouse	1400 mg/kg	---

Source: Chapter V.

TABLE 29. ADVERSE EFFECTS OF DIBROMOCHLOROMETHANE ON MAMMALS

Adverse Effect	Species	Lowest Reported Effect Level	No Apparent Effect Level
Carcinogenicity	---	No data available	---
Mutagenicity	*Salmonella typhimurium* TA 100	10 ul (vapor)	---
Teratogenicity	---	No data available	---
Chronic Toxic Effects	---	No data available	---
Median Oral Lethal Dose	Mouse	800 mg/kg	

Source: Chapter V.

TABLE 30. ADVERSE EFFECTS OF DICHLOROBROMOMETHANE ON MAMMALS

Adverse Effect	Species	Lowest Reported Effect Level	No Apparent Effect Level
Pulmonary Adenoma	Mouse	100 mg/kg i.p. x 24	40 mg/kg i.p. x 24
Mutagenicity	*Salmonella typhimurium* TA 100	50 ul (vapor)	---
Teratogenicity	---	No data available	---
Chronic Toxic Effects	---	No data available	---
Median Oral Lethal Dose	Mouse	450 mg/kg	---

Source: Chapter V.

TABLE 31. CARCINOGENIC EFFECTS OF CHLOROFORM IN RODENTS

Species	Dosage(mg/kg/day)	Response (%)	Tumor Site
NCI Study			
male rat	0	0	kidney
	90	12	
	180	26	
male mouse	0	6	liver
	138	36	
	277	98	
female mouse	0	0	liver
	238	80	
	477	95	
ICI Study			
male mouse	0	0	renal cortex
	17	0	
	60	22	

Source: Reuber (1979).

demonstrating increased renal tumors in mice, and increased hepatic tumors in male rats. The ICI data also indicate carcinogenic activity at a lower dose, but the NCI data form a larger and more consistent data base for extrapolation. It must be noted that interpretation of these results for human risk assessment is subject to a number of important qualifications and assumptions:

- Though positive carcinogenic findings exist, there have also been negative findings in tests with several species. Thus the carcinogenicity of chloroform to humans is far from certain.
- Assuming that the positive findings indeed provide a basis for extrapolation to humans, the estimation of equivalent human doses involves considerable uncertainty.
- Due to inadequate understanding of the mechanisms of carcinogenesis, there is no scientific basis for selecting among several alternate dose-response models, which yield widely differing results.
- Apart from the risk via ingestion, there may be risks due to either dermal absorption or inhalation of chloroform. However, toxicological data corresponding to these routes are not available for extrapolation purposes.

In order to deal with the large uncertainties inherent in extrapolation to humans, three commonly-used dose-response models have been applied in order to establish a range of potential human risk.

The first step in extrapolation of laboratory data is to determine the equivalent human dose. Reitz et al. (1978) showed that consideration of metabolic rates in rodents led to a more consistent interpretation of laboratory dose-response data than did the U.S. EPA method of correcting for surface area. They argue that humans are less sensitive to chloroform than rodents due to their slower metabolic rate (they maintain that the effects of chloroform are due to a toxic metabolite), and that past efforts at extrapolation have over-estimated the human risk. Accordingly, the rodent doses have been used as a basis for extrapolation in this analyses, without an attempt to convert them to a human equivalent dose. If a surface area conversion factor were introduced, it would decrease the equivalent human dose by a factor of 6 for rat data or 14 for mouse data; thus the conversion would imply considerably higher human risk.

The three dose-response models used to extrapolate human risk were the linear "one-hit" model, the log-probit model, and the multistage model. The latter is actually a generalization of the one-hit model, in which the hazard rate was permitted to be a quadratic rather than a linear function of the dose. All of these models are well known in the literature, and a theoretical discussion may be found in Arthur D. Little (1980). The one-hit models assume that the probability of a carcinogenic response is described by

$$P \text{ (response at dose X)} = 1 - e^{-h(x)}$$

where h(x) is the "hazard rate" function. The log-probit model assumes that human susceptibility varies with dose, according to a log-normal distribution. Due to their differing assumptions, these dose-response models usually give widely differing results when effects data are extrapolated from high laboratory doses to the low doses typical of environmental exposure.

The results of these extrapolations are shown in Table 32 for human exposures ranging from 0.01 mg/day to 10 mg/day. The linear model may be applied to several different groups of data, yielding a range of risk estimates. The best, and most conservative, fit was obtained using the female mouse data for liver cancer, which indicate a coefficient of about 8.6×10^{-5} increase in risk per mg/day increase in human dose. The log-probit extrapolation was performed using a unit slope with respect to the log-dose, which is generally accepted as a conservative procedure. Again, a wide range of estimates can be derived by selecting different groups of data. In order to provide a less conservative estimate of the risk, the male rat data were also utilized for kidney cancer, which predicted risks considerably lower than did the female mouse data. Finally, the multistage model was fit to the combined data for liver cancer in male and female mice.

3. Literature Review of Carcinogenic Risks of Chloroform

Since chloroform was first identified in drinking water in 1974, there has been a great deal of interest in the assessment of carcinogenic risk from trihalomethane exposure (Stokinger 1977, Tardiff 1977, NAS 1977, NAS 1978, Reitz et al. 1978, U.S. EPA 1979). These analyses contain widely varying results, which are discussed briefly below.

Tardiff (1977) used four different models for extrapolation of carcinogenic effects observed in laboratory animals at high doses to effects that may be anticipated at low doses, but did not convert data from one species to another. His analysis was based upon a maximum human dosage of 0.01 mg/kg chloroform per day, and utilized the NCI data on the carcinogenicity of this chemical. His estimates, based on four different extrapolation models, range from 0 to 0.84 additional cancers per million population each year. This is equivalent to a maximum of 60 lifetime tumors per million population at a dose of 0.7 mg/day, which agrees with the estimates in Table 32. Tardiff concludes that between 0% and 1.6% of cancer incidence in liver or kidneys may be attributable to chloroform in drinking water.

The National Academy of Sciences (1978) risk estimation was based on the multistage model of Guess and Crump, and a species conversion of

TABLE 32. PROBABLE UPPER BOUNDS ON EXPECTED EXCESS TUMORS PER MILLION POPULATION DUE TO CHLOROFORM EXPOSURE

Extrapolation Model	Exposure level (mg/day)			
	0.01	0.1	1	10
Linear Model [1]	0.86	8.6	86	860
Log-probit Model [1]	N	0.3	32	1300
Log-probit Model [2]	N	N	0.8	72
Multi-stage Model [3]	.06	.65	6.5	65

Note: Use of a dose conversion factor would increase all estimates by an order of magnitude

N = negligible

[1] Based on NCI data for female mouse.

[2] Based on NCI data for male rat (renal tumors).

[3] Based on NCI data for male and female mouse.

carcinogenicity data based on surface area. Using the NCI carcinogenicity data, the authors of the NAS study found that an oral dose of 1 ug chloroform per day resulted in an estimated lifetime risk of cancer in a 70-kg man of as much as 2×10^{-6}. This is considerably greater than the estimate of Tardiff, when one considers the extremely low dose assumption. However the majority of this difference is due to the surface area conversion factor, which Tardiff did not include. The estimates in Table 32 would be increased by about an order of magnitude if that conversion factor were used.

4. Human Exposure Scenarios

Table 33 estimates chloroform exposures for five hypothetical exposure situations: a rural area with and without a chlorinated drinking water supply, an urban setting, an industrial setting, and maximum exposures for an adult and child. A number of assumptions have been used to construct the total exposure estimates. First, 100% absorption has been assumed for oral and inhalation routes. Second, the carcinogenic activity of chloroform has been assumed to be similar for these routes, thus allowing the summation of exposures for purposes of risk evaluation. There are no data to support the validity of these assumptions, but they permit consideration of the relative contributions of various exposure routes to total risk. For the rural, urban, and industrial settings, the concentrations chosen are meant to represent typical levels for these areas. The maximum values represent maximum concentrations for all exposure routes.

As can be seen in Table 33, in areas where drinking water is chlorinated, drinking water is the predominant route of exposure. However, in urban areas, inhalation represents an important additional exposure route. Swimming in chlorinated pools may represent another important exposure route. What portion of the U.S. population may fall into each of the five categories is unknown, and there are certainly other situations that are not represented in Table 33. Nevertheless, this table is meant to illustrate a range of typical exposures.

The maximum risks of cancer were estimated for the five exposure conditions by use of the multistage model results shown in Table 32.

5. Other Trihalomethanes

Table 34 summarizes estimates for known routes of exposure to other trihalomethanes. Risk estimates of the type made for chloroform cannot be made for the other trihalomethanes since information on exposure and effects are lacking. The typical levels of exposure are much lower than for chloroform; however, exposure in a few locations is high relative to chloroform. Very little information is available on the effects of bromoform, dibromochloromethane, and bromodichloromethane for man. The only basis for comparison among the trihalomethanes is the oral LD_{50} for mice, which shows chloroform to be the least toxic (Bowman et al. 1978). Until the carcinogenesis bioassays for these other chemicals are completed, no conclusive statements can be made about risk to man.

TABLE 33. ESTIMATED EXPOSURE OF MAN TO CHLOROFORM

Exposure Situation	Exposure in mg/day (% of total)					Probable Maximum Associated Risks (Lifetime Cancer risk per capita)
	Drinking Water	Food	Inhalation	Dermal Contact	Total (max)	
Rural area no chlorination	0 (0) [1]	0.0006 - 0.04 (100)	.002 (0)	0 (0)	0.04	0.26×10^{-6}
Rural area chlorination [2]	0.02 - 0.13 (60)	0.0006 - 0.04 (18)	.002 (9)	0.03 (13)	0.2	1.3×10^{-6}
Urban	.03 - 0.2 (67) [3]	0.0006 - 0.04 (13)	0.02 (6)	0.05 (14)	0.3	2.0×10^{-6}
Industrial [4]	0.03 - 0.2 (25)	0.0006 - 0.04 (5)	0.5 (60)	0.05 (6)	0.8	5.2×10^{-6}
Maximum	1.2 (46)	0.04 (2)	1 (38)	0.3 (12)	2.6	16.9×10^{-6}
Child - maximum	0.5 (19)	0.04 (2)	1 (38)	1.1 (41) [5]	2.6	47.3×10^{-6} [6]

[1] Percent of total (using maximum values) percentages may not add to due to rounding.
[2] Assumes median level of chloroform in rural areas.
[3] Assumes chloroform concentration of 0.1 mg/l.
[4] Assumes concentration of 50 ug/m^3 24 hrs/day.
[5] Includes swimming.
[6] Assumes a 25 kg child.

Source: See Chapter V.

TABLE 34. ESTIMATED HUMAN EXPOSURE TO BROMOFORM, DIBROMOCHLOROMETHANE, AND BROMODICHLOROMETHANE

	Exposure (mg/day)					
	Drinking Water		Dermal Contact		Total	
	Median	Max.	Typical	Max.	Typical	Max.
Bromoform	0.007	0.6	0.001	0.8[1]	0.008	1.4
Dibromochloromethane	0.007	0.6	0.001	0.07	0.008	0.7
Bromodichloromethane	0.002	0.4	0.003	0.04	0.005	0.4

[1] This is for child swimming in saline pool 2 hrs/day.

Source: Chapter V.

C. AQUATIC BIOTA

The complete lack of effects data for bromodichloromethane and dibromochloromethane renders a risk analysis for aquatic life impossible. Although monitoring and effects information on chloroform and bromoform are extremely limited, some tentative conclusions can be drawn.

On a nationwide scale, no aquatic populations appear to be exposed consistently to harmful levels of either chloroform or bromoform. Anderson _et al_. (1979) state that the acute toxicity levels found in their freshwater fish bioassays "are orders of magnitude above the maximum level (24.7 mg/l) found in chlorinated water samples taken across the U.S." However, ambient levels of chloroform between 100 mg/l and 1,000 mg/l have been measured, and the occurrence of spills and discharges from industries may result in temporary and localized high concentrations that could be hazardous to aquatic life. Unfortunately, monitoring data for all of the trihalomethanes are so scarce that it is not possible to identify any specific regions that have a potential for high levels of exposure to biota.

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